EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1 CASES**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

NOTICE OF ADOPTION OF PRIOR EXPERT REPORTS AND TESTIMONY OF PEGGY PENCE, Phd, RAC, FRAPS

Comes now, the Plaintiffs, and hereby designate Dr. Peggy Pence's prior expert reports, attached hereto as Exhibit 1[1], as her general expert reports to be used at the discretion of the individual plaintiffs in the cases designated in Wave 1, Wave 2, and any future waves of Ethicon cases designated by the Court.

Dated: February 1, 2016

Respectfully submitted,

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[1] Exhibit 1, Report from *Bellew*, 7/17/2014.

PEGGY PENCE, PhD, RAC, FRAPS
EXPERT WITNESS REPORT

RE: ETHICON, INC., ETHICON WOMEN'S HEALTH AND UROLOGY, a Division of Ethicon, Inc., GYNECARE, AND JOHNSON & JOHNSON
(Collectively referred to in this Report as Ethicon)

OUTLINE OF CONTENTS

List of Key Abbreviations

AE	Adverse Event
AHWP	Asian Harmonization Working Party
BLA	Biologics License Application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	Confidence Interval
DDSA	Device Design Safety Assessment
DDUPSA	Division of Device User Programs and Systems Analysis
DFU	Directions for Use
DIA	Drug Information Association
FDA	U.S. Food and Drug Administration
FDAMA	FDA Modernization Act of 1997
FDCA	Federal Food, Drug, and Cosmetic Act
FRAPS	Regulatory Affairs Professionals Society Fellow
FTC	Federal Trade Commission
GAO	Government Accountability Office
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GLP	Good Laboratory Practice
HHS	Department of Health and Human Services
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
IFU	Instructions for Use
ISO	International Organization for Standardization
IVS	Intravaginal Slingplasty
MAUDE	Manufacturer and User Facility Device Experience Database
MDA	Medical Device Amendment
MDR	Medical Device Reporting
NB	Nota Bene
NDA	New Drug Application
NSE	Not Substantially Equivalent
OCRA	Orange County Regulatory Affairs Discussion Group
ODE	Office of Device Evaluation
ORR	Overall Residual Risk
OTC	Over-the-Counter
PDP	Product Development Protocol
PHN	Public Health Notification
PMA	Premarket Approval Application
POP	Pelvic Organ Prolapse
PSI	Prolapse Symptom Inventory
QOL	Quality of Life
QSR	Quality System Regulation
RAC	Regulatory Affairs Certification
RAPS	Regulatory Affairs Professionals Society
RCT	Randomized, Controlled Clinical Trials

RMR	Risk Management Report
SAE	Serious Adverse Event
SE	Substantially Equivalent
SG2	GHTF Study Group 2
SMDA	Safe Medical Devices Act of 1990
SUI	Stress Urinary Incontinence
TVM	Trans-Vaginal Mesh
TVT	Tension-free Vaginal Tape
UDI	Urinary Distress Inventory
US	United States of America
UTI	Urinary Tract Infection

PEGGY PENCE, PhD, RAC, FRAPS
EXPERT WITNESS REPORT

ETHICON, INC., ETHICON WOMEN'S HEALTH AND UROLOGY, a Division of Ethicon, Inc., GYNECARE, AND JOHNSON & JOHNSON
(Collectively referred to in this Report as Ethicon)

I. CREDENTIALS AND METHODOLOGY

A. Credentials: Qualifications and Experience

I have more than 40 years of experience in the research and development of traditional pharmaceuticals, biotechnology-derived therapeutics (biopharmaceuticals), and medical devices, including in vitro diagnostics. I began my career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical and regulatory affairs. I subsequently held project management and clinical management positions, from 1983 to 1992, at a number of emerging-growth companies, including Serono Laboratories (U.S. start-up), Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc.

In 1992, I founded a consulting firm that was incorporated in 1995 as Symbion Research International, Inc., a full-service contract research organization (CRO) and consulting firm. I have been President and Chief Executive Officer since that time. In this position, I provide advice, guidance, and product development services to pharmaceutical/biopharmaceutical and medical device companies in the areas of strategic planning, preclinical testing, clinical trials design and conduct, and regulatory matters involving the U.S. Food and Drug Administration (FDA), as further discussed below.

Over the course of my career, I have worked with more than 80 companies and over 90 medical devices, pharmaceuticals (drugs), and biopharmaceuticals (biologic therapeutics), including combination products (e.g., device-drug combination products). I have guided and coordinated product development activities from manufacturing process development through marketing plans and have led development programs for a number of novel therapeutics and medical devices. My medical device experience encompasses all Classes of medical devices: Classes I, II and III. I have broad experience spanning multiple therapeutic areas, including women's health, neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology. As regards women's health and wound healing and of particular relevance to the subject matter of this Report, I have designed clinical trials for diseases of the female genital system and have been involved in both preclinical and/or clinical testing of novel medical devices and biologics for wound healing applications, including both deep wounds and surgical incisions.

Notably, the product materials I have reviewed for this Report are the same types of materials I have either prepared or reviewed to assure their accuracy, completeness, and regulatory compliance during the course of my professional career. Further, Ethicon's responsibilities about which I have opined are the same types of responsibilities I have executed over the course of my career in medical product development. I have been an integral or leading member of multiple product development teams to determine the testing requirements for medical devices and drugs/biologics and to make decisions concerning whether additional testing and, if so, what types of additional testing were needed based on initial results of product testing. I have advised manufacturers on the adequacy of proposed medical device labeling. I have also contributed substantially to the development and content of product labeling, including for medical devices. For example, I have prepared clinical study reports and summarized key findings, including safety information, for inclusion in labeling. Further, I have written a number of Investigator's Brochures, which have been termed proto-labeling, because the Investigator's Brochure is the premarketing forerunner of the product package insert and provides the same types of information as the package insert, including adverse reactions, contraindications, warnings and precautions, to advise physicians and other healthcare practitioners of information important to their safe and effective use of medical products. I have analyzed safety information available from clinical trials, the scientific and medical literature, and postmarketing experience to provide this information to the U.S. Food and Drug Information (FDA) and to physicians and other healthcare practitioners to enable their safe and effective use of medical devices and drugs/biologics. I have submitted safety alerts to FDA and physicians about new and important product safety information.

Additionally, I have prepared marketing materials detailing product information. In so doing, I assured the accuracy and fair balance of the safety and effectiveness information presented. Similarly, I have advised companies on the appropriateness of information in press releases and other corporate documents to ensure any potentially misleading or improper information was excluded.

The above is a brief overview of my professional experience relevant to this Report. Further details are described below.

I have performed due diligence evaluations of potential new products to advise sponsor companies or research institutes on product development requirements, including preclinical and clinical testing needs and also regulatory pathway and strategy. I have managed internal and extramural preclinical research programs required for support of product development and manufacturing, clinical research, and business development activities. These have included product characterization, process improvement, stability studies, bioassay development, pharmacology, and preclinical efficacy studies. Additionally, I have developed product-specific, preclinical toxicology testing plans and protocols and have overseen the conduct and reporting of these studies for FDA-regulated products. I have taught Good Laboratory Practice (GLP), which is the regulatory standard for conducting nonclinical (preclinical) laboratory studies to support applications submitted to FDA for research or marketing authorizations. In addition, I have conducted GLP audits of toxicology testing facilities.

Evaluation of preclinical safety and efficacy data are central considerations before initiating human use. Accordingly, I have designed clinical investigational plans and clinical protocols in consideration of preclinical study results, including both efficacy and toxicology data. As a key member of many product development teams, I have been instrumental in the assessment of preclinical data to determine whether the available safety information supported the transition from preclinical to clinical use. Similarly, I have evaluated both preclinical and available clinical safety data to determine whether product safety profiles supported application for marketing authorization and also product development for new clinical uses.

I have designed and managed or directed the conduct of numerous clinical studies, from first-in-man studies of novel therapeutics and medical devices to pivotal studies for marketing approval. This has included performing and/or directing the monitoring, data management, analysis, and reporting of the safety and effectiveness/efficacy data from these studies, ensuring that all activities were performed in compliance with applicable regulations, Good Clinical Practice (GCP), the international regulatory and quality standard for the conduct of clinical trials involving human subjects and other relevant FDA Guidances. Of note, I established, staffed, and directed the first Clinical Quality Assurance and Document Control department at Amgen, a leading biotechnology firm. Further, I have directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications.

I have organized and directed meetings of clinical study physicians ("investigators") at the outset of multicenter clinical trials both to obtain concurrence on complex clinical study designs and endpoints and also to instruct these physician investigators on clinical trial requirements and their obligations to comply with the clinical study protocol, all applicable regulations, and GCP. I have performed compliance (quality assurance) audits of clinical investigators' conduct of clinical trials and advised and worked with them and their clinical study staff to correct any deficiencies identified. With respect to FDA inspections of clinical studies, I have been the sponsor representative with lead responsibility for "hosting" the FDA inspection of a sponsor company and clinical investigative sites.

I have provided consultation to multiple companies to establish or evaluate their processes and procedures and, in the latter case, to implement changes necessary to achieve compliance with regulatory and industry standards. In this role, I have developed standard operating procedures and set up operations to perform all aspects of clinical studies and regulatory affairs, including the following activities, among others: clinical protocol design; writing patient informed consent forms (including all known or potential risk information); writing investigator's brochures or report of prior investigations (the forerunner of the package insert/professional labeling); clinical study monitoring and management; data tracking and management; recordkeeping; and reporting of adverse events. Such procedures at Symbion have undergone quality assurance audits by multiple sponsor companies successfully. Further, I have consulted with a multinational pharmaceutical company both to develop implementation strategy and also to implement a global clinical data management system.

I have managed coding of adverse events (using dictionaries designated for regulatory activities) for worldwide clinical programs for the purpose of safety evaluations and regulatory reporting and have collected, investigated, evaluated, and reported safety data to fulfill both premarketing and postmarketing regulatory obligations. I have advised physician investigators of updated safety information: (i) in the context of providing updated investigator's brochures (which contain similar contents as eventual, professional product labeling [to the extent of known information], in order to provide for safe and effective use of the investigational product); and (ii) through required serious adverse event reports to advise physicians (as well as FDA) of new, critical safety information concerning serious risks with use of the investigational product. In the postmarketing setting, I also have directed the updating of postmarketing surveillance procedures and audited postmarketing adverse reaction records for regulatory compliance. Additionally, I have evaluated post-marketing utilization data.

I have reviewed or contributed substantially to the development of product labeling, including not only adverse reaction content but also contraindications and warnings, nonclinical toxicology and clinical studies information, and product use instructions. I have prepared product launch "backgrounders" for marketing programs and critically reviewed press releases of sponsor companies and other corporate documents prior to their release to ensure any potentially misleading or improper information is excluded.

I have served as the U.S. Agent or authorized representative for FDA matters for both medical device and drug companies, with responsibility for FDA communications and, in the case of medical device companies, for establishment registration and device listing. I have prepared and made numerous regulatory submissions of multiple types to FDA, including premarketing and postmarketing submissions, both for medical devices and drugs/biologics. Additionally, I have advised sponsor companies regarding a broad scope of regulatory requirements, including adverse event reporting, the content of adverse reactions in labels and corrective and preventive actions to address FDA inspectional findings. I have represented sponsor companies during many face-to-face meetings and teleconferences with FDA.I have served on the Board of Directors or Advisory Board for multiple organizations, including the Biotechnology and Health Programs Advisory Board, California State University Channel Islands (CSUCI); the Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB); and CompassioNow (formerly CareNow Foundation, the purpose of which is to provide medical care to the world's least served). At CSUCI, I also have served as an Advisor for the Master of Science in Biotechnology (MS Biotech) team projects, a curriculum requirement in an academic or industrial location. I have developed and teach a graduate level course titled "Clinical Trials and Quality Assurance" in the CSUCI MS Biotech program curriculum. As part of this course, I instruct my students on ethics in medical product development and the importance of obtaining and evaluating adequate preclinical safety data before transitioning to human use and assign them case studies relevant to this topic for critical evaluation and class presentation. Additionally, I have developed and taught a course titled "Clinical Trials Project Management: Managing Clinical Trials" for graduate level students enrolled in either the Program for Applied Biotechnology Studies or the Certificate in Clinical Trials Project Management Program at California State University, Fullerton. I also have served as guest lecturer for the MS Biotech program, CSUCI.

I have often been an invited speaker at industry conferences or workshops on topics current to the development of medical devices, drugs and biologics and have often provided instruction on Good Clinical Practice and other medical product development topics: at sponsor-company, in-house training programs; workshops and seminars; as a guest lecturer and instructor in university graduate or professional programs (as discussed above). I founded the Drug Information Association (DIA) Sub-group and Advisory Committee on Biotechnology and chaired DIA workshops on biotechnology in 1991 and thereafter from 1993 annually through 2001. I have served on the Regulatory Training Course Faculty for the Drug Information Association. I have been an instructor on the medical device premarketing regulations (2008-2009) and postmarketing regulations (2009) for the Orange County Regulatory Affairs Discussion Group (OCRA) course for regulatory professionals preparing to take the U.S. Regulatory Affairs Certification (RAC) examination.

I am RAC-certified, which means I hold the U.S. Regulatory Affairs Certification (RAC, certifying knowledge of U.S. regulations). The RAC credential is the only certification specifically for regulatory professionals in the healthcare product sector. It is conferred by the Regulatory Affairs Professional Society (RAPS) upon successful performance on a standardized proficiency exam, and in consideration of the applicant's education, training, and overall experience. Continuing education and assumption of leadership roles in the profession are necessary to maintain recertification, which is granted every three years, upon submission of appropriate justification. In addition to maintaining the RAC credential, in 2009 I was named a RAPS Fellow (FRAPS), a peer-reviewed credential that recognizes senior regulatory professionals based on experience, contributions, and leadership in the regulatory profession.

In sum, I have the peer-reviewed qualifications of a RAPS Fellow based on professional experience, credentials, and training. Being RAPS certified[1] and a RAPS Fellow,[2] I have achieved the highest level experience within my profession, Level IV, as outlined in the Regulatory Affairs Professional Development Framework.[3]

I earned a Bachelor of Science degree, *magna cum laude*, in Microbiology from Louisiana Polytechnic University and a Doctor of Philosophy (PhD) degree in Toxicology, with a Pharmacology minor, from Indiana University (Medical School campus). I performed my doctoral research predominantly at the Eli Lilly Laboratory for Clinical Research in Indianapolis, Indiana. My doctoral research included the planning and hands-on conduct of all aspects of three clinical pharmacology and toxicology studies. As the prior valedictorian

[1]I tested for and achieved RAPS's Regulatory Affairs Certification ("RAC"). The development of the RAC examination and selection process was based upon extensive research on the scope of practice and specific activities of the profession. This research has been replicated and updated several times, with studies extended to professionals involved with the European, US, and Canadian regulatory systems.

[2]The program recognizes professionals with over 15 years of regulatory experience for their significant contributions and leadership. Fellows receive a prestigious status and serve as important resources for strategic dialogue, mentoring, implementation of special initiatives, and international development. RAPS Fellows, *available at* http://www.raps.org/membership-amp-benefits/raps-fellows.aspx (last visited Feb. 24, 2012).

[3]The Regulatory Affairs Professional Development Framework offers a model for describing the basic body of knowledge and relevant skills of the RA profession across product lines, geographic locations and employer types at four major career stages. The skills, knowledge, and experience that I provide are reflected in this research-driven whitepaper.

for my high school, I was recognized in 2008 for my career accomplishments by induction to the Bossier High School Alumni Hall of Fame.

A copy of my current Curriculum Vitae is attached as Appendix A.

B. Methodology

I have been asked to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) in the context of the company's regulatory responsibilities as the manufacturer of the medical device GYNECARE PROLIFT +M Total, Anterior, and Posterior Pelvic Floor Repair Systems (referred to as PROLIFT or PROLIFT System[s]), indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapsed where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. All of my opinions expressed in this Report are offered to a reasonable degree of scientific and professional certainty.

During the preparation of this Report, I reviewed, consulted, and relied upon the following categories of information, listed in Appendix B:

a) Applicable statutes, regulations and guidance documents;
b) Premarket notification 510(k) number K071512 and related Ethicon and FDA correspondence;
c) Other Ethicon documents of multiple types produced in this litigation;
d) Documents located by specifically directed independent on-line searches;
e) Relevant scientific and medical literature (See Appendix C);
f) Deposition transcripts; and
g) FDA website, including the searchable 510(k) database, the Manufacturer and User Facility Device Experience Database (MAUDE) for reports of serious adverse events, and FDA's advisories and actions to address the safety issues associated with transvaginal mesh products for pelvic organ prolapse, e.g., FDA's 2008 *Public Health Notification*, 2011 *Safety Communication*, and 2011 Medical Devices Advisory Committee meeting of the Obstetrics and Gynecology Medical Devices Panel.

A number of these documents are cited in footnotes throughout this Report as primary reference materials.

In reaching my opinions, based on my synthesis, integration, and analysis of the body of relevant evidence, I brought to bear my educational background, professional training, and experience in the fields of regulatory affairs, medical product safety and efficacy, and medical product research and development. The methodology I employed and level of scrutiny applied to the totality of the evidence in this matter and in the preparation of this Report are no different than those used in my practice over the course of my career as an expert in regulatory affairs, medical product safety and efficacy, and as a researcher, educator, and scientist in general.

II. U.S. STATUTORY AND REGULATORY AUTHORITY: BASIS FOR OPINIONS

The purpose of this Section is to establish the regulatory and scientific foundation on which my professional opinions are based and set forth in this Report. Thus, I will provide a brief overview of FDA's authority to regulate medical devices, and the manufacturer's responsibility to comply with applicable regulations. I will describe device classifications and the corresponding premarket submissions required in order for a manufacturer to obtain FDA's authorization to sell a medical device in the U.S. I will complete this Section with a detailed explanation of a device manufacturer's postmarket requirements concerning (i) labeling and advertising and (ii) postmarket vigilance, or surveillance.

A. FDA Authority and Manufacturer Regulatory Compliance

The U.S. Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for regulatory oversight of the manufacture, sale, and distribution of medical devices in the United States under authority of the Federal Food, Drug, and Cosmetic Act (FDCA). Within the FDA, the Center for Devices and Radiological Health (CDRH) is the center that has the responsibility to develop and implement regulations for the purpose of protecting the public health in the field of medical devices. Ensuring optimum safety and device effectiveness, however, requires the cooperation of all stakeholders involved in the life cycle of a medical device: the manufacturer, FDA, and the end users. Each has a specific role to play in risk management.

The medical device manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device.[4] The term "person" includes individual, partnership, corporation, and association.[5] Manufacture, preparation, propagation, compounding, assembly, or processing of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in Section 201(h) of the FDCA:[6] an article intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body but which does not achieve its primary intended purposes through chemical action and is not dependent upon being metabolized to achieve its primary intended purposes.

The FDA does not design and conduct either nonclinical or clinical studies to support device safety and effectiveness; it will advise on the adequacy of studies proposed by the manufacturer and then review the completed study results and other information submitted to FDA to determine if the materials submitted support the safety and effectiveness of the device sufficiently to clear or approve the device for sale for the requested indication(s) for use. Importantly, the FDA's capacity to monitor every single medical device, or drug/biologic, postmarketing is limited. There are more than 20,000 companies worldwide that produce over 80,000 brands and models of medical devices in the U.S. marketplace,

[4] 21 CFR § 820.3(o).
[5] Section 201(e) of the Federal Food, Drug, and Cosmetic Act (FDCA).
[6] 21 CFR § 807.3(d).

according to CDRH.[7] That is why FDA depends on the cooperation and good faith of the device manufacturer to comply with FDA's regulatory decisions and applicable FDA regulations. It is the manufacturer's responsibility to ensure its devices are labeled and marketed in compliance with applicable FDA regulations.

While the FDA maintains a passive postmarketing surveillance system for safety concerns, the limitations of such a system underscore why the manufacturer is responsible for implementing a postmarket vigilance (surveillance) program. Specifically, the manufacturer must investigate and report to the FDA all serious or life-threatening adverse events about which it becomes aware if there is a reasonable suggestion that the manufacturer's device may have caused or contributed to such events. If the manufacturer becomes aware of the "need for remedial action from any information, including any trend analysis" in order "to prevent an unreasonable risk of substantial harm to the public health," the manufacturer must report such information to the FDA immediately (i.e., within five work days after becoming aware of the event).[8] The manufacturer must also maintain systems that ensure access to such adverse event information for timely follow-up and FDA inspection.[9]

In recent years, the FDA's authority and its capacity to discharge its responsibilities have been reviewed by independent agencies, including the Institute of Medicine and the Government Accountability Office (GAO). Summarily, these reports have recognized that FDA lacks the capacity to provide adequate oversight. While FDA continues efforts to address its increasingly complex public health mission of assuring medical product safety, effectiveness, and quality, the findings in these reports further emphasize why it is of critical importance for the device manufacturer to act in good faith at all times to ensure compliance with its responsibilities, as set forth in the applicable regulations, to prevent unnecessary risk to the public health.

The FDA provides multiple alternative avenues to medical device companies to assist them in interpreting any perceived grey areas in the regulations. Reasonably prudent medical device manufacturers avail themselves of these avenues provided by the FDA to ensure compliance, particularly when a question arises as to the proper course of regulatory action. These multiple alternative avenues include guidance documents and the ability to call the FDA, email the FDA, and meet with the FDA. In addition, reasonably prudent medical device manufacturers are always expected to err on the side of caution, i.e., regulatory compliance, when faced with any uncertainty or ambiguity in the regulations.

B. Device Classifications

FDA classifies medical devices into one of three regulatory classes based on the level of risk associated with use of the device and the level of control necessary to reasonably assure that the device is safe and effective for its intended use. Devices posing the lowest risk are placed in Class I and are subject to the least regulatory control. Class I devices, such as elastic bandages and tongue depressors, present minimal potential for harm to the user and are

[7] AdvaMed (Advanced Medical Technology Association). The 510(k) Process: The Key to Effective Device Regulation, 8/19/08, p.2.
[8] 21 CFR § 803.53(a).
[9] 21 CFR § 803.17(b)(4).

subject to the "General Controls" applicable to all medical devices. General Controls are the basic provisions of the 1976 Medical Device Amendments to the FDCA that provide the FDA with the means of regulating devices to ensure their safety and effectiveness. General Controls include provisions for adulteration, misbranding, establishment registration and device listing, premarket notification [510(k)], records and reports, and Good Manufacturing Practices/Quality System Regulation (QSR), among others.[10]

Class II devices pose incrementally greater risk such that the General Controls are not sufficient to provide reasonable assurance of safety and effectiveness. Class II devices are subject to "Special Controls" in addition to General Controls. Special Controls may include labeling requirements, performance standards, postmarket surveillance studies, or other controls the Agency deems necessary to provide reasonable assurance of the safety and effectiveness of the device. Ethicon's PROLIFT is a Class II device, although FDA is considering reclassification of such urogynecologic surgical meshes as PROLIFT from Class II to Class III (see Class III discussion below).[11] Electrocardiographs and powered bone drills are other examples of Class II medical devices.

The riskiest devices, such as some implants and life-supporting devices, are placed in Class III and generally are subject to Premarket Approval (PMA), which is discussed below, and means that an application must be submitted to and approved by FDA before the device may be legally marketed.

C. The PreMarket Review Process: 510(k) vs. PMA

In general, unless exempt under FDA regulations, devices are subject to one of two types of FDA premarket review before they may be legally marketed in the United States. Class I and II devices subject to premarket review are required to obtain FDA clearance through the premarket notification, or 510(k) process; Class III devices are required to obtain FDA approval through the more stringent PMA process. (There is a third but infrequently used alternative, the Product Development Protocol [PDP], which combines plans for an Investigational Device Exemption [IDE] to conduct a clinical trial.) Most Class I devices and a few Class II devices are exempt from the 510(k) requirements but are not exempt from other General Controls, which are discussed in Section II.B. above. All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have establishment registration and device listing forms on file with the FDA.[12]

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, i.e., substantially equivalent (SE), as a legally marketed device. Legally marketed devices, in this context, include any device that was legally marketed prior to May 28, 1976 (i.e., a preamendments device), for which a PMA is not required, and any device which has been found SE through the 510(k) process.[13] To support substantial equivalence claims, the device that is the subject of a 510(k) must be

[10] 21 CFR § 803.3; Device Advice – General Controls for Medical Devices, US FDA/CDRH.
[11] FDA UPDATE 01/04/2012: Urogynecologic Surgical Mesh Implants.
[12] Device Advise – Class I/II Exemptions, US FDA/CDRH
[13] 21 CFR§ 807.92(a)(3).

compared to one or more similar legally marketed devices, commonly referred to as "predicate(s)." A claim of substantial equivalence does not mean the new and predicate device(s) must be identical. SE is established with respect to intended use, design, materials, manufacturing process, performance, safety, effectiveness, labeling, standards, and other characteristics, as applicable. While clinical trials generally are not necessary for 510(k) submissions, FDA may require the conduct of clinical trials to substantiate the safety and effectiveness of a device in approximately 10-15% of cases and also may require postmarket surveillance to obtain 510(k) clearance.

In addition to the traditional method of demonstrating substantial equivalence under section 510(k) of the FDCA, there are two alternative approaches that may be used, under appropriate circumstances, to demonstrate substantial equivalence: (i) "Special 510(k): Device Modification" option, which utilizes certain aspects of the Quality System Regulation, and (ii) "Abbreviated 510(k)" option, which relies on the use of guidance documents, special controls, and recognized standards to facilitate 510(k) review. In accordance with the Quality System Regulation,[14] manufacturers must establish and follow a systematic set of pre-production design controls when initially designing medical devices or when making subsequent modifications to those designs. If a manufacturer is intending to modify its own legally marketed device and the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device, then summary information that results from the design control process can serve as the basis for 510(k) clearance, and the "Special 510(k): Device Modification" option may be utilized.[15]

Further, FDA has provided guidance to assist the medical device manufacturer to decide when a change to an existing device already in commercial distribution represents a significant change that requires a 510(k) premarket notification,[16] i.e., a change that could significantly affect the safety or effectiveness of the device or a major change in the intended use of the device.[17] "The type of modifications addressed in the draft guidance include labeling changes, technology or performance specifications changes, and materials changes. When making the decision on whether to submit a 510(k), the manufacturer's basis for comparison of any changed device should be the device described by the cleared 510(k)...The guidance includes a main flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device... If a manufacturer's consideration of all proposed changes results in a decision merely to document the decision-making, they should document the application of the model along with the necessary records of the validation of changes to the device. In those circumstances where the proposed change is not addressed in the flowchart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific guidance exists or if additional help is available."[18]

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[14] 21 CFR Part 820: Quality System Regulation.
[15] The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance, US FDA/CDRH, March 20, 1998
[16] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997
[17] 21 CFR § 807.81(a)(3).
[18] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.

A device may not be marketed in the U.S. until the 510(k) applicant receives a letter (i.e., order) declaring the device substantially equivalent, thereby "clearing" the device for marketing. This is an important distinction in that the device is not technically "approved" by the FDA as with a PMA but instead is said to be cleared, or 510(k)-cleared, for marketing. A substantially equivalent determination means that the new device is at least as safe and effective as the predicate(s), specifically, that the new device has:

(1) The same intended use and the same technological characteristics as the predicate(s); or

(2) The same intended use and different technological characteristics, and the information submitted to FDA:
   a. Does not raise new questions of safety and effectiveness; and
   b. Demonstrates that the new device is at least as safe and effective as the predicate device(s).

Technically, by regulation[19] the FDA has 90 days to review the 510(k) and issue a SE or not substantially equivalent (NSE) determination. If the FDA determines that a device is NSE (novel), it is considered Class III and will require a PMA prior to marketing. At this point, the 510(k) sponsor has the following options: (1) cease plans to market the device; (2) request reclassification; (3) submit a request for evaluation of the automatic Class III designation; (4) present new evidence (data) in support of a 510(k) clearance; or (5) proceed to develop the device through the PMA route. A class II device that is introduced into commercial distribution without a required 510(k) clearance is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

A PMA application is generally considered to be a more rigorous process than the 510(k) and is analogous to the New Drug Application (NDA) or Biologics License Application (BLA) that must be submitted for review and approval prior to marketing for drugs and biologics, respectively. The PMA is generally required for Class III devices that are determined to be either novel or that pose a significant risk of illness or injury.[20] Approval hinges on a demonstration of safety and effectiveness through the presentation of valid scientific evidence. Most often, this path requires the conduct of prospective controlled clinical trials conducted in accordance with the strict Good Clinical Practice (GCP) standards established by the FDA and the International Community. By regulation[21] the FDA has 180 days to review a PMA and issue a decision concerning approval of the application. In general, a Class III device that is introduced into commercial distribution without an approved PMA is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

[19] 21 CFR Part 807.
[20] 21 CFR Part 814.
[21] 21 CFR § 814.40.

D. Determination of Safety and Effectiveness

Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective for its conditions of use. Valid scientific evidence may include evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

There is reasonable assurance that a device is safe when valid scientific evidence exists to support a determination that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. Types of evidence that may be submitted to FDA to demonstrate there is reasonable assurance that a device is safe include nonclinical investigations, including both in vitro studies and also studies using laboratory animals, and clinical trials using human subjects.

E. Device Label, Labeling, Advertising, and Misbranding

The General Controls applicable to all devices include provisions for proper labeling and misbranding. The Federal Food, Drug and Cosmetic Act (FDCA) is the law under which the FDA takes action against manufacturers for labeling and advertising violations concerning products it regulates, including medical devices.

1. Applicable Definitions

The laws enacted by the U.S. Congress concerning products regulated by the FDA are implemented by the FDA as enforceable regulations. Together, these laws and implementing regulations define the terms that are applicable to device labeling, advertising, and misbranding. Some of the terms that are significant for purposes of this Report include the following.

1.1 Label: **Section 201(k) [21 U.S.C. 321(k)] of the FDCA defines "label" as a:**

> "display of written, printed, or graphic matter upon the immediate container of any article..."

The term "immediate container" does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear "on the outside

container or wrapper, if any there be, of the retail package of such article," or must be "easily legible through the outside container or wrapper."

1.2 Labeling: **Section 201(m) [21 U.S.C. 321(m)] of the FDCA defines "labeling" as:**

"all labels and other written, printed, or graphic matter
(1) upon any article or any of its containers or wrappers, or
(2) accompanying such article" at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

The term "accompanying" is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.[22] Training and instructional videos are considered labeling. Websites are also considered under this broad definition of labeling, and the statements a manufacturer makes about its product on websites are regulated as labeling and must be truthful and accurate.

1.3 Indications for Use

The general statement of "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.[23]

1.4 Intended Uses

The term "intended uses" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised.[24]

1.5 Contraindications

This term refers to situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed as contraindications. For example, if hypersensitivity to an ingredient in the device has not been demonstrated, it should not be listed as a contraindication.[25] Furthermore, should a medical device manufacturer have information that its medical device does not

[22] Device Advice – Labeling Requirements, US FDA/CDRH.
[23] Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo.
[24] 21 CFR § 801.4; Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo
[25] 21 CFR § 801.4; Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo

perform well in certain patient populations, it should list that information in the contraindications section.

1.6 Directions for Use (DFU) (or Instructions for Use [IFU])

This means the providing of directions to the practitioner or layman (e.g., patient), as appropriate, so that s/he can use the device safely and for the purposes for which it is intended. "Directions for Use" also include indications for use and appropriate contraindications, warnings, precautions, and adverse reaction information. Directions for Use requirements applicable to prescription devices appear throughout 21 CFR Part 801.[26]

1.7 Fair Balance

For advertising and promotional materials, this term means that advertisements must communicate fairly and in a balanced manner information relating to side effects and contraindications and information relating to effectiveness of the product.[27] In other words, information about side effects and contraindications must be comparable in depth and detail with claims for safety and effectiveness.

1.8 Prescription Device

By definition under 21 CFR § 801.109, this is a device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except under the supervision of a practitioner licensed by law to direct the use of the device, and hence for which "adequate directions for use"[28] cannot be prepared.

2. General Device Labeling: 21 CFR Part 801

General labeling requirements for medical devices have been established in 21 CFR Part 801. Guidance on "Indications for Use," "Contraindications," "Warnings," "Precautions," and "Adverse Reactions" paraphrase applicable provisions in the labeling requirements for prescription drugs.[29]

A premarket notification must normally only contain proposed labeling sufficient to describe the device's intended use, as discussed in the "Blue Book" 510(k) Memorandum #K86-3 dated June 30, 1986.[30] Accordingly, a 510(k) finding of substantial equivalence does not connote approval of the proposed labeling. However, in the case of devices with special labeling requirements and devices for which inclusion of specific directions for use, contraindications, warnings, etc., in the labeling may be critical to a finding of equivalence, CDRH's Office of Device Evaluation (ODE) 510(k) labeling review includes an evaluation of compliance of the proposed labeling or portions thereof, as appropriate.

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[26] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[27] 21 CFR §§ 202.1(e)(5) and (6).
[28] 21 CFR § 801.5.
[29] 21 CFR Part 201; Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[30] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.

In contrast, specific labeling is approved as part of a PMA. While, FDA will approve a PMA on the basis of draft final labeling if the only deficiencies concern editorial or similar minor deficiencies in the draft final labeling, PMA approval depends on incorporation of the specific labeling changes exactly as directed and the manufacturer is required to submit to FDA a copy of the final printed labeling before marketing.[31] Labeling changes that affect the safety or effectiveness of a device require a PMA supplement and can be done without FDA approval via a Special PMA Supplement only when such modifications are based on newly acquired information and evidence of a causal relationship between the product and a safety signal. New information "must reveal risks of a different type or greater severity or frequency than previously included in submissions."[32,33] Importantly, routine review of patient labeling for all original PMAs and panel-track supplements will be conducted by the FDA Division of Device User Programs and Systems Analysis (DDUPSA) when human factors for the usability of the device need to be considered.[34]

3. The Meaning of Intended Use

To determine whether or not a new device has the same intended use as a predicate device, CDRH assesses any difference in label indications based on the safety and effectiveness questions they may raise. As described in Section II.C., "same intended use" is a key determinant in assessment of substantial equivalence. CDRH considers such points as condition or disease to be treated or parts of the body or types of tissue involved, etc. If a new device is determined to have the same intended use, CDRH may then proceed to determine whether or not it is substantially equivalent. Devices that do not have the same intended use cannot be substantially equivalent.[35]

4. Promotion and Intended Use

Products are cleared or approved for certain intended uses. Change in Intended Use may require a new clearance or approval. New Intended Use can be created by:

(1) Labeling, advertising, or promotional claims;
(2) Oral statements;
(3) Manifestations of objective intent;[36]
(4) Expressions;
(5) Circumstances of distribution; and
(6) Offering with knowledge of use.[37]

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[31] FDA Device Advice: Device Regulation and Guidance. PMA Labeling http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissio ns/PremarketApprovalPMA/ucm050390.htm.
[32] 21 CFR § 814.39 PMA Supplements.
[33] Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision. Dec 11, 2008 http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089274.htm#4e.
[34] FDA Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #69-3).
[35] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.
[36] 21 CFR §§ 201.128, 801.4.
[37] 21 CFR § 801.4.

5. Labeling and Advertising (General Device Labeling: 21 CFR Part 801)

According to an appellate court decision: "Most, if not all, labeling is advertising. The term 'labeling' is defined in the FDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."[38]

While advertising and promotion are not defined in the FDCA and FDA regulations for medical devices, FDA interprets any activity used by the sponsor to create an interest in the company's products, including the Internet, as advertising.[39]

Jurisdiction over medical device advertising is split between the FDA and the Federal Trade Commission (FTC). The FTC has primary oversight responsibility for the advertising of non-restricted devices. The FTC prohibits advertising that is false and misleading and requires substantiation of all claims that are made in advertisements.[40] With regard to the advertising of medical devices, the FTC has defined substantiation as requiring balanced, scientific evidence in the form of well-controlled clinical studies.

Except in extraordinary circumstances, FDA cannot require prior approval of the content of any advertisement except in the case of any printed matter which FDA determines to be labeling as defined in Section 201(m) of the FDCA.[41]

6. Misbranding

Section 502 of the FDCA (21 U.S.C. § 352) contains provisions on misbranding and false or misleading labeling. A device is misbranded if:

(1) Its labeling is false or misleading in any particular;[42]
(2) Its advertising is false or misleading in any particular;[43]
(3) It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling;[44]
(4) Its labeling does not bear adequate warnings;[45]
(5) There is a failure to furnish any materials or information requested by or under Section 519 of the FDCA on reports and records;[46] and
(6) There is a failure to have a necessary 510(k) clearance.[47]

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[38] *United States v. Research Laboratories, Inc.*, 126 F.2d 42, 45 (9th Cir. 1942), *cert. denied*, 317 US 656 (1942).
[39] FDA Docket No. 2005N-0354.
[40] 15 U.S.C. § 45.
[41] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[42] FDCA § 502(a).
[43] FDCA § 502(j).
[44] 21 U.S.C. § 352.
[45] FDCA § 502(f)(2).
[46] FDCA § 502(t).
[47] FDCA § 502(o).

Pursuant to the FDCA § 201(n), a device is misbranded when there is a failure to reveal material facts.

In summary, prescription medical devices such as Ethicon's GYNECARE PROLIFT are misbranded if their labels do not bear information for use including indications, effects, routes, methods, frequency and duration of administration (as applicable), and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the devices can use them safely and for the purpose for which they are intended, including all purposes for which they are advertised or represented,[48] or if there is a failure to obtain the necessary 510(k) clearance.

A medical device may be misbranded not only if the actual label contains false or misleading representations, but also if the device's advertising fails to reveal facts material to the representations made or consequences that may result from the use of the product under the conditions of use prescribed in the labeling or advertising or under such conditions of use as are customary or usual.[49] Labeling and advertising must therefore present a fair balance of information relating to the side effects and effectiveness of the product.

7. False or Misleading Labeling

The phrase "false or misleading" is not confined in meaning to untrue, forged, fraudulent, or deceptive. The word "misleading" in the FDCA means that labeling is deceptive if it creates or leads to a false impression in the mind of the reader. A "false impression" may result not only from a false deceptive statement, but may also be instilled in the mind of the consumer by ambiguity, misdirection, or failure to inform the consumer of facts that are relevant to those statements actually made**. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims.**[50]

Examples of false or misleading labeling include, among others:

(1) Unsubstantiated claims of therapeutic value;
(2) Expression of opinion or subjective statements; and
(3) Failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion.[51]

8. Warnings

Product labeling is a primary cornerstone of managing product safety, because communication of serious risk is critical to prevent or mitigate product risk. Thus, labeling content, including warning statements when required to protect users, is a key factor in determining whether there is reasonable assurance that a device is safe and effective for its intended use.

[48] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[49] 21 U.S.C. § 321(n).
[50] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.
[51] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.

Warning statements on "Instructions for Use" should be delineated by underlining, bold print, boxing, etc. The purpose of "Warnings" is to describe serious adverse reactions and potential safety hazards, the limitations of device use due to such concerns, and steps that should be taken if they occur. A causal relationship need not have been proved.
As discussed in FDA's guidance document titled "Guidance on Medical Device Patient Labeling," there are four elements generally recognized by the courts and research as necessary for an effective warning:

(1) Signal word, i.e., WARNING;
(2) Hazard avoidance directive to give clear instructions to the user on how to avoid the hazard;
(3) Clear statement of the nature of the hazard associated with the warning that characterizes the severity and the likelihood; and
(4) Consequences, specifying the serious adverse events, potential safety hazards and limitations in device use that result if users do not follow instructions.[52]

In other words, for patient labeling, warnings must be set forth in plain language in a manner designed to be understood by the lay person without a medical background. A warning is insufficient if the reader does not understand or appreciate the consequences of failure to comply with the Warning. Hazard alert research has shown that giving a clear idea of the risk has a significant effect on readers.[53]

F. Manufacturer Serious Adverse Event Reporting Requirements

1. Historical Perspective

Since 1984, domestic manufacturers of medical devices have been required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions. The statutory authority for the Medical Device Reporting (MDR) regulation is Section 519(a) of the Federal Food Drug & Cosmetic Act (FDCA). On September 14, 1984 (49 FR 36326), FDA issued Medical Device Reporting (MDR) regulations for manufacturers and importers under the FDCA and the Medical Device Amendments of 1976 (Public Law 94-295). To correct weaknesses noted in the 1976 amendments and to better protect the public health, Congress enacted the Safe Medical Devices Act of 1990 (SMDA) (Public Law 101-629). SMDA imposed significant new reporting requirements on the medical device industry, including user facilities and distributors of medical devices. To implement SMDA and changes mandated by the Medical Device Amendments of 1992 (Public Law 102-112) (amending certain provisions, Section 519 of the FDCA, relating to reporting of adverse events), FDA published the final MDR regulation for user facilities and manufacturers in the Federal Register on December 11, 1995. The new MDR regulation became effective on July 31, 1996.

[52] Center for Devices and Radiological Health, U.S. Food and Drug Administration. Guidance on Medical Device Patient Labeling, April 19, 2001.
[53] Center for Devices and Radiological Health, U.S. Food and Drug Administration. Guidance on Medical Device Patient Labeling, April 19, 2001.

The FDA Modernization Act of 1997 (FDAMA) (Public Law 105-115) was signed on November 21, 1997, and FDAMA changes to medical device adverse event reporting (MDR) became effective on February 19, 1998. On January 26, 2000, changes to the implementing regulations, 21 CFR Parts 803 and 804, were published in the Federal Register to reflect these amendments in the FDCA. Also, Part 804, Medical Device Distributor Reporting, was removed. The MDR Rule changes became effective March 27, 2000.

2. Postmarket Vigilance/Surveillance - Medical Device Reporting (MDR) Regulation: 21 CFR Part 803

The purpose of Medical Device Reporting is to protect the public health by ensuring that devices are not adulterated or misbranded and are safe and effective for their intended use. The MDR regulation provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order that safety problems may be detected and corrected in a timely manner. While the requirements of the regulation can be enforced through legal sanctions authorized by the FDCA, accomplishing the objectives of the regulation is dependent on the compliance and cooperation of manufacturers and other affected entities such as user facilities, importers, and distributors.

Reporting device problems to the FDA is a critical communication link to ensure the safety and effectiveness of marketed medical devices. FDA continually evaluates the Manufacturer and User Facility Device Experience Database (MAUDE), which includes reports of adverse events involving medical devices, to detect potential hazards, or safety signals. The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[54]

2.1 Applicable Definitions

The FDA defines the terms that are used in the MDR regulation. Some of the terms that are significant for purposes of this Report include:

2.1.1 *MDR reportable event (or reportable event)*: An event that user facilities (e.g., hospital, ambulatory surgical facility, outpatient treatment facility) become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or an event that manufacturers become aware of that reasonably suggests that one of their marketed devices:

i. May have caused or contributed to a death or serious injury, or
ii. Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

2.1.2 *Malfunction* means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended

[54] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR § 801.4.

2.1.3 *Become aware* means that an employee of the manufacturer has acquired information that **reasonably suggests** a reportable adverse event has occurred.

1) For an event that is required to be reported within 30 calendar days, a manufacturer is considered to have become aware of the event when any of its employees becomes aware of the reportable event.
2) For an event reportable within 5 work days, the manufacturer is considered to have become aware of the event when any of its employees with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or whose duties relate to the collection and reporting of adverse events, becomes aware, from any information, including any trend analysis, that a reportable MDR event or events necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health.

2.1.4 *Reasonably suggests* means any information, including professional, scientific, or medical facts, observations, or opinions, that may reasonably suggest that a device has caused or may have caused or contributed to a MDR reportable event.

2.1.5. *Caused or contributed* means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of labeling or user error.

2.1.6. *Serious injury* means an injury or illness that:
1) Is life-threatening;
2) Results in permanent impairment of a body function or permanent damage to a body structure; or
3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

2.1.7 *Permanent* means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

2.1.8 "The term '*user error*' means any error made by the person using the device. A user error may be the sole cause or merely contribute to a reportable event. As with the 1984 regulation, there is the requirement for reports of certain adverse device events caused by user error. For example, device injuries attributed to user error may show that the device is misbranded within the meaning of section 502(f) of the FD&C Act [21 U.S.C. 352(f)] in that the device fails to bear adequate directions for use or adequate warnings. Reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries. (Refer to the FR preamble, page 63583, Final Rule, December 11, 1995."[55]

[55] Medical Device Reporting for Manufacturers, Prepared by Division of Small Manufacturers Assistance Office of Communication, Education, and Radiation Programs, FDA CDRH, March 1997.

With these definitions in place, I will now address the manufacturer reporting requirements for the investigation, evaluation and reporting of serious adverse events.

3. Overview of Manufacturer Reporting Requirements

Part 803 of the Code of Federal Regulations Title 21 (21 CFR Part 803) is the implementing regulation for Medical Device Reporting. This Part establishes the requirements for medical device reporting for medical device manufacturers, importers, user facilities, and distributors. Regulations from this Part that are applicable to my analysis and professional opinions herein include the following:

(1) Deaths and serious injuries that a manufacturer's device has or may have caused or contributed to must be reported to the FDA;
(2) Certain device malfunctions must also be reported;
(3) The device manufacturer is required to establish and maintain adverse event files;
(4) The device manufacturer is required to submit supplemental/follow-up reports when new (required) information is obtained that was not available when the initial Medical Device Report was submitted to FDA.

4. Reporting of Adverse Events

A manufacturer is required to investigate, evaluate and submit reports of adverse events to the FDA pursuant to 21 CFR § 803.10(c); § 803.20(a), (b)(3); §803.50(a), (b); §803.52; §803.53; §803.56.

4.1 30-Day Reports

A manufacturer must submit reports of individual adverse events no later than 30 calendar days after the day that the manufacturer becomes aware of information from any source that reasonably suggests that a device may have caused or contributed to a death, serious injury, or a malfunction that, should it recur with the device in question or a similar device, would be likely to cause or contribute to a death or serious injury.[56]

4.2 5-Day Reports

In the case of a reportable event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health, the manufacturer must submit reports of individual adverse events no later than five (5) work days after the day the manufacturer becomes aware of the event. The manufacturer may become aware of the need for remedial action from any information, including any trend analysis.

[56] 21 CFR § 803.10(c)(1); § 803.20(b)(3); § 803.50(a).

Additionally, the FDA may make a written request for the submission of a 5-day report. In such case, the manufacturer must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request, which time period may be extended if FDA determines it is in the interest of the public health.[57]

4.3 Mandatory Reporting Information Requirements

The manufacturer must submit such mandatory reports using the FDA Form 3500A.[58] On this form, the manufacturer must provide all information required that is reasonably known to the manufacturer.

4.3.1 *Reasonably known* is considered to include the following information:

a) Any information that the manufacturer can obtain by contacting a user facility or other initial reporter;

b) Any information in the manufacturer's possession;

c) Any information that the manufacturer can obtain by analysis, testing, or other evaluation of the device.[59]

4.3.2 The manufacturer is responsible for obtaining and submitting to FDA information that is incomplete or missing from reports submitted by user facilities and other initial reporters.[60]

4.3.3 The manufacturer is responsible for conducting an investigation of each event and evaluating the cause of the event. If the manufacturer cannot submit complete information on a report, it must provide a statement explaining why this information was incomplete and the steps taken to obtain the information.[61]

4.3.4 If the manufacturer later obtains any required information that was not available at the time the initial Medical Device Report was filed, it must submit this information in a supplemental report.[62]

5. When is a Manufacturer Excused from Submitting an MDR?

A manufacturer does not have to report an adverse event if it has information that would lead a person who is qualified to make a medical judgment reasonably conclude that a device did not cause or contribute to a death or serious injury.[63] Persons qualified to make a medical judgment include physicians, nurses, risk managers, and biomedical engineers. The manufacturer must keep in its MDR event files the information that the qualified person used to determine whether or not a device-related event was reportable.

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[57] 21 CFR § 803.10(c)(2); § 803.20(b)(3); § 803.53.
[58] 21 CFR § 803.20(a).
[59] 21 CFR § 803.50(b)(1).
[60] 21 CFR § 803.50(b)(2).
[61] 21 CFR § 803.50(b)(3).
[62] 21 CFR § 803.50(b)(3).
[63] 21 CFR § 803.20(c)(2).

A manufacturer is not required to submit a Medical Device Report if it determines that the information received is erroneous in that a device-related adverse event did not occur.[64] The manufacturer must retain documentation of such report in its MDR files for the time periods specified below under "Records Retention."[65]

When a manufacturer receives reportable event information for a device it does not manufacture, it is not required to submit a Medical Device Report, but the manufacturer must forward this information to the FDA with a cover letter explaining that it did not manufacture the device in question.[66]

6. The Submission of a MDR is Not an Admission of a Causal or Contributory Relationship

21 CFR § 803.16 makes clear that the manufacturer's submission of a MDR or release of that report by FDA is not necessarily an admission that the device, or the manufacturer or its employees, caused or contributed to the reportable event. The manufacturer does not have to admit and may deny that the report or information submitted under 21 CFR Part 803 constitutes an admission that the device, the manufacturer or its employees, caused or contributed to the reportable event. This regulation underscores the purpose of Medical Device Reporting, even when the manufacturer is in doubt that its device caused or contributed to a reportable event, i.e., to ensure that signals are not overlooked but can be identified and acted upon by the company and the FDA in a timely manner.

7. Requirements for Written MDR Procedures and Recordkeeping

7.1 Standardized Procedures

The manufacturer must develop, maintain, and implement written MDR procedures to identify, communicate, and evaluate adverse events. There must be a standardized review process for determining when an event meets the criteria for reporting under 21 CFR Part 803, and the information must be submitted to the FDA timely. Records must be maintained for all information that was evaluated to determine if an adverse event was reportable, and all Medical Device Reports and information submitted to FDA must be maintained. The company must have systems that ensure timely access to these records for follow up and inspection by FDA.[67]

7.2 Establishing and Maintaining MDR Event Files

The manufacturer of a medical device is required to establish and maintain MDR event files. All MDR event files must be clearly identified and maintained to facilitate timely access.[68]

"MDR event files" are written or electronic files and must contain:

1) Information in the manufacturer's possession or references to information related to the adverse event, including all documentation of deliberations and decision-

[64] 21 CFR § 803.22(b)(1).
[65] 21 CFR § 803.18(c).
[66] 21 CFR § 803.22(b)(2).
[67] 21 CFR § 803.17.
[68] 21 CFR § 803.17.

making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable under 21 CFR Part 803; and

2) Copies of all MDR forms, as required by 21 CFR Part 803, and other information related to the event that the manufacturer submitted to FDA.

A manufacturer may maintain MDR event files as part of its complaint file, under 21 CFR Part 820, if the MDR reportable events are prominently identified as such.

7.3 Records Retention

The medical device manufacturer must retain a MDR event file relating to an adverse event for a period of two (2) years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater.[69] Accordingly, in the case of a permanently implantable medical device, the regulations require the manufacturer to maintain MDR event files indefinitely.

8. Global Harmonization Task Force (GHTF) Guidances: Postmarket Vigilance

The Global Harmonization Task Force (GHTF)[70] was conceived in 1992 to address the growing need for international harmonization in the regulation of medical devices, with two principal aims: (i) enhancing patient safety and (ii) increasing access to safe, effective, and clinically beneficial medical technologies worldwide. GHTF is a partnership between regulatory authorities and the regulated medical device industry and is comprised of five Founding Members: United States, European Union, Canada, Australia, and Japan. Beginning in 2006, membership expanded to include three Liaison Body members: International Organization for Standardization (ISO), International Electrotechnical Commission (IEC), and Asian Harmonization Working Party (AHWP). A primary purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety as well as the effectiveness/performance and quality of medical devices. This is accomplished through the development and dissemination of harmonized guidance documents concerning basic regulatory practices. These documents are developed by different GHTF Study Groups and provide a model for the regulation of medical devices that can then be adopted/implemented by national regulatory authorities.

The GHTF Study Group 2 (SG2) is responsible for developing guidance documents concerning medical device vigilance such as medical device reporting and postmarket surveillance. Specifically, SG2 is charged first with reviewing current adverse event reporting, postmarket surveillance and other forms of vigilance for medical devices and performing an analysis of different requirements amongst countries with developed device regulatory systems and then using this information to develop harmonized guidances for data collection and reporting systems. A number of the finalized SG2 guidance documents provide medical device industry standards of practice applicable to the subject matter of this Report, e.g.: (i) Adverse Event Reporting Guidance for the Medical Device

[69] 21 CFR § 803.18(c).
[70] Global Harmonization Task Force Website: http://www.ghtf.org/.

Manufacturer or its Authorized Representative;[71] (ii) Manufacturer's Trend Reporting of Adverse Events;[72] and (iii) Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices.[73]

Timothy A. Ulatowski, former Director, Office of Compliance, Center for Devices and Radiological Health (CDRH), U.S. Food and Drug Administration, advised device manufacturers at the 2009 AAMI/FDA Conference on Medical Device Standards and Regulation to keep apprised of the GHTF, as its new standards and guidance documents could influence FDA regulation, stating that "Companies need to become more aware because we're all moving in this direction." "GHTF is becoming the global nomenclature."[74]

9. Underreporting of Adverse Events

The FDA relies on the MedWatch postmarketing surveillance program to monitor drug (and biologics) adverse reactions through a database known as the Adverse Event Reporting System (AERS), as well as the MAUDE database for Medical Device Reporting. Despite these mandatory and voluntary reporting programs, postmarket adverse event underreporting is pervasive throughout the system. The FDA recognizes that only a small percentage of the total burden of adverse events is captured through MedWatch and "generally assumes that only 1 in 10 adverse (drug) events is reported."[75] Although device-related adverse events are at least as common as drug-related events in the hospital, in-hospital device use and device-related problems are poorly documented.[76,77] This vast under-recognition of device-related problems may help to explain why the rate of postmarket adverse event reporting is even bleaker for medical devices, with congressional reports estimating that as few as 1 in 100 medical device reportable events are actually reported.[78] Bright and Shen estimated that, at the national level, 14% of adverse medical device effects were reported to CDRH in 2003. However, since this estimate was based on hospital discharge records, the true rate of underreporting for this population is unknown but certainly less than 14%.[79] Other reasons for underreporting of adverse events include, lack

[71] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative. June 29, 1999.
[72] GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events. January 2003.
[73] GHTF FINAL DOCUMENT: Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices. November 30, 2006.
[74] Ulatowski: GHTF to Guide FDA Regulations, Guidances. *The QMN Weekly Bulletin.* April 17, 2009; Vol 1 No 16.
[75] Drazen JM et al. Current adverse event reporting systems. Adverse Drug Event Reporting: The Roles of Consumers and Health-Care Professionals: Workshop Summary, Forum on Drug Discovery, Development, and Translation. *National Academy of Sciences* 2007.
[76] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.
[77] Samore MH et al. Surveillance of medical device-related hazards and adverse events in hospitalized patients. *JAMA* 2004;291:325-334.
[78] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.
[79] Bright RA and Shen J. Use of a free, publicly-accessible data source to estimate hospitalizations related to adverse medical device events. Draft manuscript, 2005.

of reporting by health care providers due to lack of knowledge or fear of blame and lack of reporting to FDA.[80]

III. CLINICAL BACKGROUND: REPAIR OF PELVIC ORGAN PROLAPSE

A. Introduction

Surgical mesh has been used since the 1950s to repair abdominal hernias. Traditional treatment options for pelvic organ prolapse (POP) include hysterectomy, colporrhaphy (plication of pubocervical or rectovaginal fascia), sacrocolpopexy (suturing of vaginal apex to the sacral promontory using either mesh or fascial bridge) performed either abdominally or laparoscopically and sacrospinous fixation (securing the vaginal apex to the sacrospinous ligament). Mesh products were introduced as supporting materials in the surgical treatment of POP to address the high levels of recurrence rates associated with traditional repairs.

In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for transvaginal repair of POP. Initially, surgeons cut the mesh to the desired shape and placed it through a corresponding incision. Now pre-shaped mesh kits that allow for placement of a lightweight mesh implant via a transvaginal procedure are available. These kits now include tools to aid in the delivery and insertion of the mesh. Surgical mesh materials can be divided into four general categories:

- non-absorbable synthetic (e.g., polypropylene or polyester)
- absorbable synthetic (e.g., poly(lactic-co-glycolic acid) or poly(caprolactone))
- biologic (e.g., acellular collagen derived from bovine or porcine sources)
- composite (i.e., a combination of any of the previous three categories)

POP occurs when the pelvic floor tissues that hold the pelvic organs in place become weakened or stretched, often from childbirth. This causes the pelvic organs to bulge (or prolapse) into the vagina. The pelvic organs sometimes prolapse past the vaginal opening, and more than one pelvic organ can prolapse at the same time. The organs involved in POP may include the bladder (cystocele), the uterus (procidentia), the rectum (rectocele), the top of the vagina (apical prolapse) or the bowel (enterocele). POP can be asymptomatic for some women, but for others, it may negatively impact the quality of life by causing pelvic discomfort and interfering with sexual, urinary and defecatory function, as well as other daily activities. It is estimated that 10 to 30 per 100,000 women will require surgical intervention and of these, approximately 30% will require additional surgery for recurrence and/or incontinence.

[80] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.

The placement of surgical mesh is intended to increase the longevity of POP repairs. In general, mesh products for POP repair are configured to match the anatomical defect they are designed to correct. Mesh can be placed in the anterior vaginal wall to aid in the correction of cystocele (anterior repair), in the posterior vaginal wall to aid in correction of rectocele (posterior repair), or attached to the top of the vagina to correct uterine prolapse or vaginal apical prolapse (apical repair). Surgical mesh can also be placed through the abdomen (transabdominally) to correct apical prolapse. This latter procedure is known as sacral colpopexy and was described using prosthetic slings in 1974. High success rates were reported in the 1980s, and sacral colpopexy has become accepted in the gynecologic community as an effective surgical means to correct POP.

B. Food and Drug Administration Literature Review

There are few randomized controlled clinical trials comparing mesh to traditional surgery (no mesh). In an Executive Summary prepared by the FDA for the September 8-9, 2011, Obstetrics & Gynecology Devices Advisory Committee Meeting, the FDA states that a review of the literature for repair of POP with surgical mesh found only 22 reports from randomized clinical trials.

The majority of the studies evaluated anterior prolapse repair, followed by posterior and apical vaginal repair. The duration of follow-up ranged from perioperative (intraoperative to 48 hours post-operative) to 60 months. Most studies reported adverse events and outcomes of perioperative period to 12 months postoperative. Only five studies reported a follow-up period beyond 12 months.

The FDA review identified a number of limitations with the existing literature: (1) results reflect both primary and repeat prolapse repairs; (2) most studies involve concomitant surgical procedures; (3) adverse event reporting is inconsistent; (4) inclusion/exclusion criteria are incompletely documented; (5) the majority of randomized clinical trials are not evaluator-blinded or adequately powered; and (6) few studies extend beyond two years.

In addition, the literature on POP repair largely represents studies in which the primary endpoint was ideal anatomic support, defined as prolapse Stage 0 or 1 (i.e., the lowest point of prolapse is more than 1 cm proximal to the vaginal opening). This outcome is not based on a correlation with symptomatology and is not necessary for most women to achieve symptomatic relief.

C. Clinical Trials Comparing POP Correction With and Without Mesh

The vast majority of studies reported in the literature dealing with POP repair have been uncontrolled trials, retrospective studies, underpowered studies, case series or incomplete/preliminary findings such as presented at clinical conferences. Furthermore, the primary outcome measure was nearly always based on anatomical (objective) cure rate or recurrence rate and often patient-reported outcomes of quality of life data were either underreported or not reported. Few trials attempted to blind either patients or evaluators. Another weakness is the absence of long-term follow-up studies. Mesh materials and surgical techniques have also changed over the decades of mesh use, and, therefore, outcomes reported in the earlier literature may not be relevant today.

Reports of five prospective, randomized, controlled clinical trials of POP surgery with mesh versus without mesh were reviewed for this clinical summary. The articles were published between 2009 and 2011. Two of the studies enrolled patients with anterior prolapse, two with anterior and/or posterior prolapse, and one was simply described as "urovaginal or vaginal" prolapse. The meshes used in these trials were all non-absorbable synthetic polypropylene.

In a multicenter, parallel-group, randomized, controlled trial comparing the Gynecare Prolift Anterior Pelvic Floor Repair System Kit (Ethicon) to traditional colporrhaphy in women with prolapse of the anterior vaginal wall (cystocele), 200 women underwent repair with the mesh kit and 189 underwent traditional colporrhaphy.[81] Overall, 16% underwent surgery as a secondary procedure because of prolapse recurrence. At the 2-month follow-up, success rates were 73% for the mesh group and 49% for the colporrhaphy group. At the 1-year follow-up, success rates were 61% for the mesh group and 35% for the colporrhaphy group. Between the 2-month and 1-year follow-up, Urinary Distress Inventory (UDI) scores deteriorated in both groups, but more so for the colporrhaphy group. At the 1-year follow-up, symptoms of stress urinary incontinence were significantly worse in the mesh group, but obstructive symptoms were less bothersome. Pain during sexual intercourse occurred "usually" or "always" in 2% of the patients in the colporrhaphy group and 7% of the mesh group. Forty percent of the colporrhaphy group and 48% of the mesh group were "usually" or "always" satisfied with their sexual relationships. The mesh group had significantly longer duration of surgery (56.2 vs 33.5 minutes), more intraoperative blood loss, more frequent need for intraoperative cytoscopy, and more bladder perforations than the colporrhaphy group. Inguinal pain and bladder emptying difficulties during the hospital stay were also more frequent in the mesh group. The most frequent adverse events during the first 2 months after surgery were urinary tract infections, pelvic pain and urine retention. These had resolved at the 1-year follow-up, except for one patient in the mesh group. Also, by the 1-year follow-up, 5 of 186 patients in the mesh group had undergone surgery for stress incontinence and 6 of 186 had undergone surgery to correct mesh exposure. One patient in the colporrhaphy group had undergone a second surgery due to prolapse recurrence. The authors suggest that their lower success rates were due to the inclusion of a patient-reported subjective outcome measure in the primary endpoint. The use of mesh also resulted in higher numbers of adverse events, which must be balanced against the higher success rates in a risk-benefit analysis.

A double-blind, multicenter, randomized controlled trial of traditional vaginal prolapse surgery compared to vaginal surgery using mesh (PROLIFT system) reported 3-month outcomes after surgery in women with POP-Q stages 2-4.[82] The primary success outcome was POP-Q stage 0 or 1. The need for additional surgical treatment or pessary placement for recurrent prolapse also constituted treatment failure. Patients were blinded to treatment arm, and post-surgical follow-ups at three and 12 months were performed by a blinded evaluator. Thirty-two patients were randomized to the mesh group and 33 to the non-mesh group. The planned number of patients was 90, but the study was stopped early because the number of

[81] Altman D et al. Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse, *New England Journal of Medicine* 2011;364:1826-36.
[82] Iglesia CB et al. Vaginal Mesh for Prolapse – A Randomized Controlled Trial. *Obstetrics & Gynecology* 2010;116(2 pt 1):293-303.

mesh erosions had reached a predetermined stopping point (5/32, 15.6%). Comparative analyses showed no difference in recurrence between the two groups (mesh: 19 [59%], no mesh: 24 [70%]; p = 0.28). Subjective cure of symptoms was 93.3% (mesh) versus 100% (no mesh). Quality of life endpoints were also no different between the two groups. The authors question the value of additive synthetic polypropylene mesh for vaginal prolapse repairs.

In a randomized, controlled trial comparing vaginal repair augmented by mesh (Gynemesh PS, Ethicon) with traditional colporrhaphy for the treatment of POP, 69 patients were randomized to the mesh arm and 70 were randomized to the no-mesh arm.[83] Patients and surgeons were not blinded. The primary outcome measure of success was POP-Q <2 at 12 months after surgery. At 12 months, 51/63 (81%) of women who returned for follow-up in the mesh group achieved objective success compared with 40/61 (66%) in the no-mesh group (p = 0.07). There were no statistically significant differences between groups in patient-reported quality of life measures, including sexual function. Four patients in the mesh group had mesh exposures. Although this study showed no significant reduction in recurrence with mesh augmentation, the authors note that there was a large number of patients in each group who were lost to follow-up. They conclude that a larger study is required to more conclusively assess the effectiveness and safety of mesh augmentation.

In a randomized, multicenter, controlled study, the efficacy and safety of trocar guided tension-free vaginal mesh insertion (Prolift) was compared to conventional vaginal prolapse repair in patients with recurrent POP ≥ stage 2.[84] The primary outcome was anatomic failure (POP ≥ stage 2 in the treated vaginal compartments). Anatomic outcomes were assessed by an unblinded surgeon. Ninety-seven women were randomized to the no-mesh arm and 93 to the mesh arm. Twelve months postsurgery, anatomic failure in the treated compartment was observed in 38 of 84 patients (45.2%) in the no mesh group and in eight of 83 patients (9.6%) in the mesh group (*P*<.001). Most of the "failures" had POP-Q stage 2 and did not require further intervention. Subjective improvement was reported by 64 of 80 patients (80%) in the conventional group compared with 63 of 78 patients (81%) in the mesh group. Mesh exposure was detected in 14 of 83 patients (16.9%) (7 patients at 6 months and 6 at 12 months). Nine of these patients were asymptomatic. The authors concluded that while anatomic cure rates were significantly higher in the mesh group, symptomatic improvement and quality of life were essentially the same.

A randomized, multicenter, controlled trial compared outcomes of anterior colporrhaphy with and without mesh.[85] The primary outcome measure was anatomic recurrence defined by either point Aa or Ba at ≥ stage 2 by the POP-Q system. The study was not blinded to either patients or evaluators. Three years after surgery, 40 of 97 (41%) patients in the no-mesh group had anatomic anterior wall prolapse recurrence compared with 14 of 105 (13%) in the mesh group. Nine (9%) patients in the no-mesh group and 16 (15%) in the mesh group suffered apical or posterior prolapse. There were no statistically significant

[83] Carey M et al. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. *BJOG* 2009;116:1380-1386.

[84] Withagen MI et al. Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse – A Randomized Controlled Trial. *Obstetrics & Gynecology* 2011;117(2 pt 1):242-250.

[85] Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up. *Am J Obstet Gynecol* 2010;203:235.e1-8.

differences between groups in prolapse symptoms assessed by standard questions. The mean score from the questionnaire assessing a feeling of vaginal bulge statistically favored the mesh group. Differences in bladder emptying were not statistically significant. During the 3-year follow-up, a total of 20 patients were diagnosed with mesh exposure at any visit. None of the patients had the mesh removed; treatments included topical estrogen, closure of the epithelium, and partial resection. The authors concluded that the use of mesh provides superior anatomic cure, although differences in symptom relief were minor.

D. Conclusions of Literature Review for POP Repair

Few prospective clinical trials compare no-mesh versus mesh-supported surgery for POP. Of those reviewed, the authors were in agreement that additional studies are needed to assess the risk/benefit of the use of mesh (particularly non-absorbable mesh) in the correction of POP. Some studies (prospective and retrospective) report that the use of mesh increases the cure rate based on objective criteria (POP-Q stage). However, that has not been comprehensively correlated with patient-reported quality of life outcomes. When these have been reported, there is little difference between surgical procedures using mesh and those without mesh, and the use of mesh is associated with additional complications, particularly mesh erosion. Furthermore, most published reports of clinical trials have only included a short-term follow-up. Long-term safety and efficacy studies of the use of mesh in POP have not been published. The heterogeneity in trial design and outcome measures preclude a rigorous comparison or meta-analysis of results.

Summaries of review articles and selected individual studies, including those discussed above, and case series are provided in Appendix C.

E. Ethicon Internal Clinical Study Report Summaries: Protocols Number CT-TVM001-03 and 2003-016 – Evaluation of the TVM Technique for Treatment of Genital Prolapse

Ethicon initiated two non-randomized, non-controlled studies in 2004 to evaluate a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the GYNECARE PROLIFT System that is the subject of this Report. This “prototype” mesh was provided in a similar shape to that of the PROLIFT System. Implantation instruments were not provided. One of the studies was conducted at eight investigational sites in France. The second was performed at three investigational sites in the U.S. The protocols for these studies were similar and were designed to assess the usability of the pre-cut mesh for anterior, posterior, and vault prolapse in women with symptomatic prolapse of at least ICS Stage III, using the pre-cut mesh and a transvaginal surgical technique. The primary effectiveness endpoint for both studies was the proportion of subjects in whom correction of prolapse (ICS Stage 0 or 1) was observed at 12 months post-operatively. Secondary endpoints for both studies included vaginal prolapse in the area not treated with mesh, peri- and post-operative complications, patient tolerance of the synthetic mesh, and quality of life (QOL). The U.S. study included an additional secondary endpoint: recurrence rate of vaginal prolapse in the area treated with mesh.[86] The French study differed from the U.S.

[86] ETH.MESH.02341734 at 736: Gynecare PROLIFT Instructions for Use (IFU) (in use 1 Oct 09 to 7 May 10 per IFU Index and Production Bates Range Chart).

study in that only 51 (56.7%) subjects had a transgluteal approach, while all of the total TVM repairs in the U.S. study were performed using the transgluteal approach. The remaining 39 (43.3%) patients in the French study had mesh placed by the vaginal route only.[87]

Study subjects available for follow-up at 12 months included 90 patients in the French study[88]and 85 in the U.S. study.[89] The 12-month follow-up results for the French study showed a failure rate of 18.4% with a 90% CI of 11.9-26.6,[90] with wide variation in recurrence rates observed between investigational sites.[91] Thus, the study did not meet the pre-defined primary effectiveness endpoint of a failure rate of less than 20% (upper limit of 90% CI). The secondary effectiveness parameter of failure rate at six months was 12.6% (90% CI: 7.3, 20.1).[92] Substantial improvements in QOL were observed, both in prolapse symptoms and in activities of daily living QOL scores.[93]

For the U.S. study, the reported failure rate at 12 months was 12.0% with a 90% CI of 6.7-19.6. Because the upper 90% two-tailed CI does not exceed 20%, this study provided evidence of a prolapse recurrence rate of less than 20% using the criteria outlined above. The secondary effectiveness parameter of failure rate at six months was 8.3% (90% CI: 4.0, 15.1). Substantial improvements in QOL were observed, both in prolapse symptoms and in activities of daily living QOL scores.[94]

In the French study, fewer patients reported decreased sexual activity due to prolapse at 12 months compared with baseline (6 [6.9%] vs 29 [32.2%]). However, the number of patients not having sexual activity for reasons other than prolapse was much higher at 12 months. Specifically, there were 40 sexually active patients at 12 months and 42 at six months compared with 61 at baseline. The incidence of dyspareunia in sexually active patients was 4/61 at baseline (7%), 8/42 (20%) at 6 months, and 3/40 (8%) at 12 months. An additional patient was reported as having dyspareunia at baseline but was not sexually active due to prolapse. The three cases of dyspareunia at 12 months were all new onset, while dyspareunia was resolved at 12 months in the five patients who reported the condition at baseline.[95]

Eleven (11) patients (12.6%) reported moderate or severe vaginal retraction. Visible or visible and palpable mesh exposure occurred in nine patients (10%) during the 12-month follow-up, with five (5.6%) requiring surgical intervention. One other patient had additional examinations (urethrocystoscopies, rectoscopies) but had not undergone surgery for mesh exposure. Note that palpable mesh alone was not deemed to be mesh exposure.[96] The intra-

[87] ETH.MESH.00357123 at 185: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[88] ETH.MESH.00357123 at 124: *Id*
[89] ETH.MESH.00357204 at 205: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.
[90] ETH.MESH.00357123 at 126: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[91] ETH.MESH.00357123 at 184: *Id.*
[92] ETH.MESH.00357123 at 126: *Id.*
[93] ETH.MESH.00357123 at 127: *Id.*
[94] ETH.MESH.00357204 at 208: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.
[95] ETH.MESH.00357123 at 126: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[96] ETH.MESH.00357123 at 171: *Id.*

operative complication rate was low. Urinary tract infection (15 [16.9%]) was the major post-operative complication at six weeks. Hematoma and abscess were reported by four patients (4.5%) and one patient (1.1%), respectively. One case of vesicovaginal fistula was reported and was resolved with surgery. Significantly, in the 90 patients studied, there were 27 serious adverse events (SAEs) reported, and 18 of these were considered probably related to the study device or procedure.[97] The 27 SAEs occurred in 23 patients, or 25.6% of study subjects experienced one or more SAEs. Sixty-eight (68) patients (75.6%) experienced one or more adverse events (131 total). Nine (10%) patients experienced a severe adverse event, and 45 (50%) patients required treatment for adverse event(s).[98]

In the U.S. study, there were no patients who reported decreased sexual activity due to prolapse at 12 months compared with 24 (28.2%) pre-operatively. There were more patients sexually active at 6 months (50) and 12 months (43) than at baseline (31). The incidence of dyspareunia in sexually active patients was 16/31 (51.6%) at baseline, 3/50 (6%) at six months, and 1/43 (2.3%) at 12 months. The intra-operative complication rate was low (3.5%). Post-operative complications, reported for three patients (3.5%) at six weeks, included urinary tract infection and hematoma.[99] For the 85 patients studied, there were 56 (65.9%) who reported adverse events (98 total)[100] during the 12-month follow-up period. Urinary incontinence (17 [20.0%] patients), mesh exposure (12 [14.1%] patients), and void dysfunction (9 [10.6%] patients) were the most commonly reported adverse events. Three patients required surgical management for mesh exposure. "Other adverse events were each reported in less than 10% of patients." Eleven (12.9%) patients experienced at least one adverse event that was considered to have a causal relationship to the device,[101] and 27 (31.8%) patients experienced at least one adverse event considered procedure-related.[102]

The sponsor concluded that both studies demonstrated reasonable success rates and a lower rate of recurrence/re-operation compared to other published studies. Further, the sponsor summarized the safety profile as predictable with a favorable benefit/risk ratio.[103, 104] In my professional opinion, the sponsor's conclusion that the complication rate is low in each study is not supported by the data, particularly considering there were 27 serious adverse events in 25.6% of patients in the French study, and 65.9% of patients in the U.S. study experienced adverse events, a number of which also represented serious adverse events. Although these two studies were uncontrolled, without a no-mesh group for comparison, the results are generally consistent with the conclusions from the literature review for POP repair, discussed above. Specifically, the data agree with most studies which show that mesh increases the anatomic cure rate, but the use of mesh is associated with additional complications, especially mesh erosion, which raises concern about the risk vs benefit.

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[97] ETH.MESH.00357123 at 127: *Id.*
[98] ETH.MESH.00357123 at 175: *Id.*
[99] ETH.MESH.00357204 at 208: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.
[100] ETH.MESH.00357204 at 252: *Id*
[101] ETH.MESH.00357204 at 208: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.
[102] ETH.MESH.00357204 at 252: *Id*
[103] *Id*
[104] ETH.MESH.00357123 at 127: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.

Of note, the TVM procedure used in both studies was further adapted with design of the needle and cannula to protect the attachment points for the mesh that turned out to be at risk using the TVM tools.[105,106]

IV. REGULATORY HISTORY: ETHICON'S SURGICAL AND VAGINAL MESH PRODUCTS

A. Methodology Used and Construction of Regulatory History

To review and evaluate the overall regulatory history of Ethicon's surgical mesh products, a simple search of FDA's searchable 510(k) database was conducted for the following terms:

- Ethicon
- Surgical Mesh
- Prolift
- Prolift+M
- Johnson & Johnson (J&J)

The J&J simple search was further refined using an "advanced search" for the following parameters:

- J&J, surgical mesh; 1 Jan 1998 to the present
- Ethicon, surgical mesh; 1 Jan 1998 to the present

The result of these searches is presented in Tables 1.1, 1.2, 1.3, and 1.4 and provides a hierarchic representation of the product development and predicate history that eventuated in the marketing of the GYNECARE PROLIFT total, anterior, and posterior pelvic floor repair system.

B. Overview: Regulatory History of Ethicon's Surgical and Vaginal Mesh Products

PROLENE nonabsorbable polypropylene suture, the first of Ethicon's surgical mesh product line, was initially regulated as a drug and approved by NDA 16374 prior to the enactment of the Medical Device Amendments (MDA) on 28 May 1976. Following passage of the MDA, devices that had been regulated previously as new drugs and approved under New Drug Applications (NDAs) were officially given device status as "transitional devices." A Premarket Approval application (PMA) number with "N" before the application number (which is the original NDA number) denotes a transitional device; the PMA Number for PROLENE is PMA N16374. (The original approval could not be located through online search efforts that included a search of the FDA PMA database, a general search of CDRH, a search of "drugs @ FDA" for approved drug products, and a "Google" search. However, a listing of the supplements to this PMA was found, with a December 31, 1980, decision date for Supplement 001.)

[105] ETH.MESH.00357123 at 185: *Id.*
[106] ETH.MESH.00357204 at 257: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.

Reclassification as a polypropylene nonabsorbable surgical suture class II device (21 CFR 878.5010), for use in general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures, was published in the Federal Register on May 31, 1991 (Volume 56, No. 105, Pages 24684-24685). This product is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart E, Surgical Devices, Nonabsorbable Polypropylene Surgical Suture. Also in 1991, PROLENE Polypropylene Mesh Plug W/onlay patch was cleared (510(k) number K915774) under classification regulation 878.3300: surgical mesh defined as metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples are for hernia repair, acetabular and cement restrictor mesh used during orthopedic surgery. This product also is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart D, Prosthetic Devices, Surgical Mesh. All the remaining products discussed in this review were 510(k)-cleared under the classification regulation 21 CFR 878.3300.

The first of 12 Ethicon 510(k)s (that could be identified from the 510(k) searchable database) for the repair of hernia defects was submitted to FDA in 1996 and was a modification of the PROLENE Polypropylene nonabsorbable synthetic surgical mesh. According to the 510(k) Summary of Safety and Effectiveness, the modified device has the same technological characteristics as the predicate device (i.e., no change in chemistry, material or composition), but **differs from the predicate device in the additional sizes supplied and a precut key hole shape provided as a convenience to the surgeon**.[107] In 2000, PROLENE Soft Polypropylene Mesh, which is knitted by a process which interlinks each fiber junction, **provides for elasticity in both directions** and is 50% more flexible than PROLENE, according to the description in the 510(k) Summary of Safety and Effectiveness,[108] was granted 510(k)-clearance (510(k) number K001122) based on substantial equivalence to Ethicon's PROLENE ((Polypropylene) and MERSILENE Meshes (Ethicon polyester mesh). All three of these products, i.e., PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh and Mersilene Mesh, served as the predicates for the January 2002 GYNEMESH PROLENE Soft (Polypropylene) Mesh 510(k)-clearance for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. (Emphasis added.)

In 2003, Ethicon's ULTRAPRO Mesh (510(k) number K033337), for the repair of hernia and other fascial deficiencies, was found substantially equivalent to Ethicon's VYPRO Mesh (510(k) number K001122), PROLENE Polypropylene Mesh and MERSILENE Mesh.[109] This product, as well as Ethicon's GYNEMESH (510(k) number K013718), American Medical System's APOGEE Vault Suspension System (510(k) number K040537) and PERIGEE System (510(k) number K040623) served as the predicates for the GYNECARE PROLIFT and GYNECARE PROLIFT+M total, anterior, and posterior pelvic floor repair systems, intended for tissue reinforcement and long-lasting stabilization

[107] FDA 510(k) Searchable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pd.

[108] FDA 510(k) Searchable Database: K001122 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K001122.pdf.

[109] FDA 510(k) Searchable Database: K033337 Summary of Safety and Effectiveness - **http://www.accessdata.fda.gov/cdrh_docs/pdf3/K033337.pdf.**

of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for fascial defect (510(k) number K071512).[110]

The first of six 510(k)s for GYNECARE Tension-free Vaginal Tape (TVT) System and its various modifications was granted 510(k)-clearance in 1998 (510(k) number K974098). This product is a pubourethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT device is composed of PROLENE polypropylene mesh (tape), and the mesh is covered with a polyethylene sheath with a slit in the middle.[111]

Table 1.1 Ethicon Surgical Mesh Regulatory History – Other Indications for Use (i.e., not for hernia or pelvic floor repair)

510(k) History: Regulation 878.3300

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for Use
K915774 12/24/91 03/02/92	PROLENE Polypropylene Mesh Plug W/onlay patch	Unavailable	

510(k) History: Regulation 878.5010

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for Use
K001625 5/17/00 7/10/00	Pronova Nonabsorbable Suture	Surgilene and PROLENE sutures	In general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures.

[110] FDA 510(k) Searchable Database: K071512 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh docs/pdf7/K071512.pdf.
[111] FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K974098.pdf.

Table 1.2 Ethicon Surgical Mesh Regulatory History – 510(k) History: Hernia Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K962530 6/28/96 8/9/96	Modified PROLENE Polypropylene mesh nonabsorbable synthetic surgical mesh	PROLENE polypropylene mesh nonabsorbable synthetic surgical mesh	Repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material.
K972412 6/26/97 9/10/97	PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant	Bard® Marlex® Mesh Perfix® Plug Nonabsorbable Polyproylene surgical mesh device	Repair of inguinal hernia defects, both indirect and direct.
K984220 11/25/98 2/23/99	Modification: PROLENE(Polypro-pylene) Hernia System	(Polypropylene) Hernia System	Repair of abdominal wall hernia defects.
K001122 4/7/00 5/23/00	PROLENE Soft (Polypropylene) Mesh	PROLENE (Polypropylene) Mesh and Mersilene Mesh	Repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.
K002672 8/28/00 11/22/00	Vypro Mesh	PROLENE mesh and Vicryl (Polyglactin 910) Mesh for materials and indications and Mersilene Polyester Mesh for Indications	Same (Repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.)
K010722 3/12/01 4/27/01	PROLENE (Polypropylene) 3D Patch	(Polypropylene) Hernia System and Bard Marlex PerFix Plug	Repair of inguinal (direct and indirect) and abdominal wall hernia defects.

Table 1.2 Ethicon Surgical Mesh Regulatory History – 510(k) History: Hernia Repair: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K031925 6/27/03 9/17/03	PROCEED Surgical Mesh	PROLENE Soft Polypropylene Mesh	Repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.
K033337 10/17/03 4/1/04	UltraPro Mesh	Vypro Mesh, PROLENE Polypropylene Mesh, Mersilene Mesh	Same (Repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.)
K060713 3/17/06 5/25/06	PROCEED Surgical Mesh	PROCEED Trilaminate Surgical Mesh	Same (Repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.)
K061533 6/2/06 12/11/06	PROCEED Ventral Pouch	PROLENE soft mesh, PROCEED Mesh, Bard Ventralex & Small Ventralex, Hernia Patch, Vicryl Mesh, Ethibond Polyester Suture	Repair of hernias or other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.
K070224 1/24/07 4/17/07	ULTRAPRO Plug	K033337 (Ethicon) K922916 (Bard)	Open repair of groin hernia defects.
K071249 5/7/07 6/5/07	ULTRAPRO Hernia system	PROLENE Hernia System, ULTRAPRO Mesh	Open repairs of abdominal wall hernia defects.
K093932 12/22/09 4/9/10	Physiomesh	K031925, K060713 (PROCEED), K071249 (Ultrapro hernia system), K033337 (Ultrapro Mesh)	Repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Table 1.3 Ethicon Surgical Mesh Regulatory History – 510(k) History: Pelvic Floor Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K013718 11/8/01 1/8/02	Gynemesh PROLENE Soft (Polypropylene) Mesh	PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh, and MERSILENE Mesh	Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect
K063562 11/27/06 2/26/07	Gynecare Prosima Pelvic floor repair systems	Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh, Silimed Vaginal Stent	Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor, either as mechanical support or bridging material for the fascial defect. The Systems provide maintenance of the vaginal canal during the period of healing following surgical repair of vaginal wall prolapse, while supporting position of the mesh implants.
K071512 6/4/07 5/15/08	Gynecare Prolift and Gynecare Prolift+M total, anterior, and posterior pelvicfloor repair systems	K013718 (Gynemesh Prolene Soft Mesh), K033337 (Ultrapro Mesh), K040537 (AMS Apogee), K040623 (AMS Perigee)	Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for fascial defect.

Table 1.3 Ethicon Surgical Mesh Regulatory History – 510(k) History: Pelvic Floor Repair: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K082216 8/6/08 9/5/08	Ethicon Mesh	K013718 (Gynemesh PROLENE Soft Mesh), K071512 (Prolift+M)	Same (Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for fascial defect.)

Table 1.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K974098 10/30/97 1/28/98	Gynecare TVT Tension-free Vaginal Tape	ProteGen Sling Collagen Impregnated Material	As a puburethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate the placement of the TVT device.

Table 1.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K012628 8/13/01 10/26/01	TVT System with three accessories (modification)	Gynecare Tension Free Vaginal Tape (TVT) System with Accessories: TVT resusable introducer TVT reusable rigid catheter guide Cook OB/GYN Stamey Needle	(Same)As a puburethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate placement of the TVT device.)
K033568 11/13/03 12/8/03	Gynecare TVT Obturator Device	Gynecare TVT Device	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency
K052401 9/1/05 11/28/05	Gynecare TVT Secur System	Gynecare TVT System and Gynecare TVT Obturator	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.
K100485 2/19/10 3/16/10	Gynecare TVT Exact Continence System	Gynecare TVT Tension Free Vaginal Tape (K974098)	As a suburethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.

Table 1.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K100936 4/5/10 7/1/10	Gynecare TVT Abbrevo Continence System	Gynecare TVT Obturator System (K033568)	Same (As a puburethral sling for treatment of female Stress Urinary Incontinence,resulting from urethral hypermobility and/or intrinsic sphincter deficiency.)

V. REGULATORY HISTORY: GYNECARE PROLIFT® PELVIC FLOOR REPAIR SYSTEM – MARKETING OF MISBRANDED AND ADULTERATED PRODUCT DUE TO LACK OF A NECESSARY 510(k)

A. Methodology Used and Construction of Relevant History

To review the regulatory history specific to the Gynecare Prolift Pelvic Floor Repair System, I principally looked at 510(k) applications, the documentation in Ethicon's 510(k) and related files, and the FDA's searchable 510(k) database. Additionally, I reviewed deposition testimony in which the regulatory process was discussed in some detail. The 510(k) clearances for Prolift, the subject of this report, Prolift+M, and the predicates for these devices are included in Tables 1.2 and 1.3. The 510(k)-cleared indications for use, the 510(k) number, the date FDA received the 510(k), and the date FDA cleared the device for marketing (510(k)-clearance) are provided for each of these mesh products.

B. GYNEMESH PROLENE Soft (Polypropylene) Mesh

Gynemesh Prolene Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair is constructed of knitted filaments of extruded polypropylene identical in composition to that used in Ethicon's PROLENE Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. As described in the 510(k) Summary of Safety and Effectiveness for the GYNEMESH PROLENE Soft (Polypropylene) Mesh, "the mesh affords excellent strength, durability and surgical adaptability, with sufficient porosity for necessary tissue ingrowth....The mesh is constructed of reduced diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE Mesh." When the same material has been used as a suture, it has been reported to be non-reactive and to retain its strength indefinitely in clinical use. This mesh is knitted by a process that interlinks each fiber junction and provides for elasticity in both directions, permitting the mesh to be cut into any desired shape or size without unraveling. Purportedly, "[t]he bi-directional elastic property allows adaption [sic] to various stresses encountered in the body."[112]

[112] FDA 510(k) Searchable Database: K013718, GYNEMESH PROLENE Soft (Polypropylene) Mesh - http://www.accessdata.fda.gov/cdrh_docs/pdf/K013718.pdf.

FDA received Ethicon's 510(k) premarket notification (510(k) number K013718) on November 8, 2001, and cleared the GYNEMESH PROLENE Soft (Polypropylene) Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair for marketing on January 8, 2002, for the following Indications for Use: Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.[113] Notably, the predicate devices for GYNEMESH PROLENE Soft (Polypropylene) Mesh were 510(k)-cleared for hernia repair and repair of other fascial deficiencies, as shown in Table 1.2: PROLENE Soft (Polypropylene) Mesh; PROLENE (Polypropylene) Mesh; and MERSILENE.

GYNEMESH PROLENE Soft (Polypropylene) Mesh is provided in two sizes. For sacrocolpopexy procedures, there is the GYNECARE GYNEMESH™ PS Non-absorbable PROLENE™ soft mesh extra large (25cm x 25cm) designed for abdominal approaches. For vaginal pelvic organ prolapse procedures, there is the GYNECARE GYNEMESH™ PS non-absorbable PROLENE™ soft mesh (10cm x 15cm) designed for vaginal approaches.[114]

C. GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems

On February 8, 2005, Sean O'Bryan, Senior Project Manager, Regulatory Affairs at Ethicon, issued a notification to customers stating that "GYNECARE PROLIFT* Pelvic Floor Repair Systems (PROLIFT) is considered a line extension of the existing marketed GYNECARE GYNEMESH* PS device. GYNECARE GYNEMESH PS received 510(k) clearance on January 8, 2002 (K013718). According to the FDA Guidelines, GYNECARE PROLIFT is covered by this existing approval..."[115] The GYNECARE PROLIFT was launched for marketing in March 2005. The original "Regulatory Strategy – Project D'Art," dated September 23, 2003, addressed the plan to design, manufacture, and market the PROLIFT using GYNECARE GYNEMESH PS in new pre-cut shapes with combinations of guide needles, fasteners, and a fastener delivery device to facilitate placement of the precut mesh shapes[116] and reported that "According to the FDA Guidelines, adding new sizes (or shapes) does not require a new 510(k)."[117] However, just a few months prior to Ethicon's decision not to seek 510(k) clearance for the PROLIFT System, i.e., in June 2003, Ethicon documented that the regulatory pathway in the U.S. would be 510(k) submission and clearance prior to marketing what later became the PROLIFT device.[118]

The Regulatory Strategy revision for the PROLIFT device (Project D'Art) dated October 6, 2004,[119] documents that three kits were to be offered and included a "kit" registration justification: 1) Anterior implant, 2) Posterior implant, and 3) Total implant. Each kit was to include GYNECARE GYNEMESH PS that had been precut in the shapes shown below for the appropriate

[113] Indication for Use Statement: K013718, GYNEMESH PROLENE Soft (Polypropylene) Mesh - http://www.accessdata.fda.gov/cdrh_docs/pdf/K013718.pdf.
[114] Ethicon website for Professional Resources, Gynecare Gynemesh PS: http://www.ethicon360emea.com/products/gynecare-gynemesh-ps.
[115] ETH.MESH.00031323: February 8, 2005, Memo to Customer, copy to Regulatory File, Re: GYNECARE PROLIFT considered line extension of GYNECARE GYNEMESH.
[116] ETH.MESH.00011698: Regulatory Strategy – Project D'Art, September 23, 2003, prepared by Sean O'Bryan.
[117] ETH.MESH.00011698 at 699: Regulatory Strategy - Project D'Art, September 23, 2003, prepared by Sean O'Bryan.
[118] ETH.MESH.03803493.ppt and ETH.MESH.03803484.ppt: June 27, 2003 Gynecare Worldwide presentations, Anterior TVM (Porthos) and ATHOS/ARAMIS/PORTHOS, Concept → Feasibility.
[119] ETH.MESH.00552393-394: Regulatory Strategy Revision Log.

type of repair, plus three disposable instruments anatomically designed to facilitate accurate introduction and implantation of the mesh: 1) PROLIFT Guide, 2) PROLIFT Cannula, and 3) PROLIFT Retrieval Line. According to this regulatory strategy document, there were to be no changes to the GYNEMESH device other than that it would be "offered in several dimensions to accommodate different types of prolapse (1 for each kit)." [120] Ethicon certified that "all components of these kits are 1) exempt from premarket notification (consistent with the exemption criteria described in the classification regulations and the limitations of exemptions from Section 510(k) of the Act (21 CFR Section 807.85); 2) found to be substantially equivalent through the premarket notification process under the Food, Drug and Cosmetic Act for the use for which the kit is intended."[121]

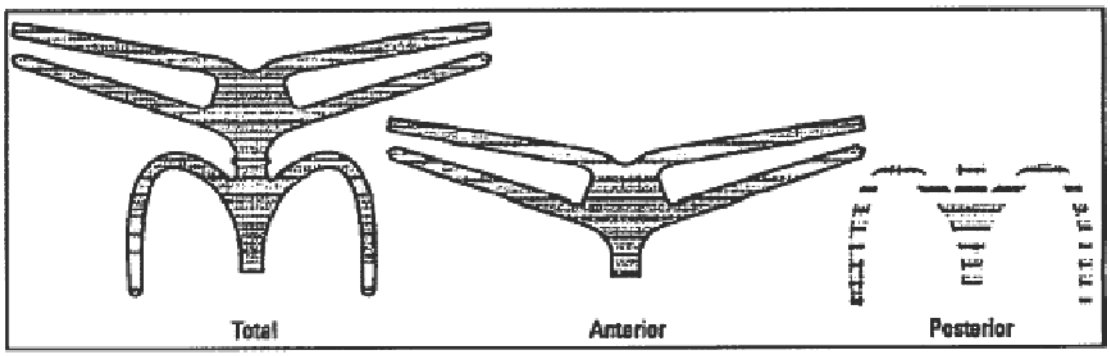

Figure 1 – Mesh Implants (Total, Anterior, and Posterior)

Ethicon appears to contend that the PROLIFT kit components are exempt from the requirements of premarket notification under 21 CFR § 807.85 because such devices are custom devices. Ethicon's certification in this regard indicates a fundamental misinterpretation of the custom device provisions of the FDCA and implementing regulations; please see the March 15, 2003, Warning Letter included as Appendix D to this Report for a relevant discussion confirming my assessment.[122] The PROLIFT kits do not meet the criteria for a custom device and as such are not exempt from compliance with the 510(k) premarket notification requirements. Moreover, Ethicon purports that the **"Instruments** are classified be [sic] the FDA as a [sic] Class I sterile surgical instruments and are exempt from premarket notification in accordance with 21 CFR parts 807.85 and 884."[123] On my review of the device classification regulations included under 21 CFR Part 884 - - Obstetrical and Gynecological Devices, I find no classification category that is pertinent to the instruments included in the PROLIFT kits. Regardless, the instruments that were anatomically designed for the PROLIFT kit are considered components/accessories to a classified device (the surgical mesh) and take on the same classification as the "parent" device.[124]

[120] ETH.MESH.00552393 at 394: Regulatory Strategy Revision Log.
[121] ETH.MESH.00552393 at 395: Regulatory Strategy Revision Log
[122] FDA Warning Letter, March 15, 2002, to Endotec Incorporated: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2002/ucm144815.htm
[123] ETH.MESH.00552393 at 395: Regulatory Strategy Revision Log.
[124] Content of a 510(k)": http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142651.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=content%20of%20a%20510k&utm_content=1.

Further, Ethicon relied on the FDA Guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)[125] in its decision not to submit a 510(k) for its new PROLIFT device. This guidance addresses three types of device modifications: labeling changes, technology or performance specifications changes, and materials changes. To aid the manufacturer in determining when a 510(k) is required for a change to an existing device, the guidance includes a series of flowcharts to guide the manufacturer through key decision-making criteria concerning whether a modification of any of these three types exceeds the 21 CFR § 807.81(a)(3) threshold, i.e., "could significantly affect the safety or effectiveness of the device."

Using the flowcharts for assessing labeling changes and technology or performance specifications changes from the K97-1 guidance discussed above, Ethicon summarized its decision not to file a 510(k) for the PROLIFT device as follows: "if the dimensional specifications change but do not affect indications for use, if no clinical data is necessary to establish safety and effectiveness (S&E) for the purpose of substantial equivalence, and if the design validation does not raise new issues of S&E, a new 510(k) is not necessary and documentation is sufficient to sell and market the subject device. In addition, changes to the warnings and precautions revised the labeling for clarity to insure safer or more effective use, a new 510(k) is not necessary and documentation is sufficient to sell and market the subject device."[126] Further, it was determined that new clinical data was not necessary to establish safety and effectiveness, based on the Clinical Expert Report (1/14/05) of Charlotte D. Owens, Worldwide Medical Director – Gynecare.[127]

In my professional opinion, a reasonably prudent medical device manufacturer would have submitted a 510(k) application for PROLIFT, and Ethicon's decision not to submit a 510(k) for the PROLIFT was a violation of the standard of care for a number of reasons. Notably, while Ethicon was advised of this by FDA in 2007 after submitting the 510(k) for the PROLIFT+M, the reasons supporting that a 510(k) submission for the PROLIFT was required were known to Ethicon prior to its marketing of the PROLIFT. Examples of such knowledge from Ethicon's communications/documents are discussed below.

1) A novel surgical protocol was developed for using the PROLIFT device to treat pelvic organ prolapse: TVM (Trans-Vaginal Mesh) Prosthetic Repair Technique.[128] GYNECARE GYNEMESH was pre-cut according to a standard template[129] and supplied as the investigational device to demonstrate the feasibility of this novel surgical technique for treatment of the anterior wall, posterior wall, and vaginal vault in clinical studies conducted in France and the USA.[130] The TVM procedure was "further adapted with design of the needle and cannula to protect the attachment points for the mesh that turned out to be at risk using the TVM tools."[131]

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[125] 510(k) Memorandum #K97-1: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.
[126] ETH.MESH.00011731 at 733: Regulatory Strategy Review, GyneCare Prolift Pelvic Floor Repair System (Project D'Art), 6/13/2007.
[127] ETH.MESH.00011731-732: Regulatory Strategy Review, GyneCare Prolift Pelvic Floor Repair System (Project D'Art), 6/13/2007.
[128] ETH.MESH.00357123 at 137: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[129] ETH.MESH.00357123 at 146: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[130] ETH.MESH.00357123 at 137: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.
[131] ETH.MESH.00357123 at 185: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM

2) The standard GYNECARE GYNEMESH product was provided as a 10cm x 15cm rectangular piece of mesh for vaginal approaches.[132] No specially designed instruments or surgical protocol was provided with or required for the GYNEMESH product.

3) Notably, in October 2004, the Director Marketing Europe for GYNECARE, Steve Bell, reported the "top 10 key learnings from the first TVM-Training course in Lille."[133] Among these were the following:

- "The consensus is that some doctors will need more than one exposure to TVM surgery before they feel confident to be able to start the procedure (even those with high skill sets)."[134]
- "It was shown that a key part of the training is in the 'Feel' of the needle passages to ensure they pass in the right place through the right structures. Cadavers may not give this full experience and where possible the training surgeons need to get hands on in live surgery by either 'scrubbing in' where allowed. Or by having the preceptor go to their institution to help guide the passage of the needles."[135]
- "The TVM represents a MAJOR mind shift on several key aspects of prolapse surgery that may require a greater shift in thinking: No resection of the excess vagina: Uterine conservation where possible: No suturing of the mesh to the vagina or lateral structures: Passage THROUGH the sacrospinal ligaments: -- All of these are new concepts and will require good back up during the education process to explain why they are essential to good results."[136]
- "The dissection of the posterior compartment for this procedure is significantly different to that for either standard sacro-spinous fixation procedures (Richter) or for even Posterior IVS....It was considered more technically challenging than they had thought."[137]
- "There is a wide range of opinion on how many cases will be needed for a preceptor to become sufficiently proficient to teach this procedure. Anything from 5 cases to 3 months (30 cases) to assess the procedure and learn the tricks."[138]
- The TVM procedure was seen unanimously as a very innovative and novel way to do POP."[139]

4) The Final PROLIFT Device Design Safety Assessment (DDSA, Revision C), dated February 25, 2005, while it found the device design safe for use,[140] described the medical impact of the device system to the current standard of care as representing "a combination and optimization of techniques that have evolved and are now combined to address the totality of vaginal repair procedures."[141] Notably, the "Use Related Hazard Worksheet" documents, in response to the

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technique for treatment of genital prolapse.

[132] Ethicon website for Professional Resources, Gynecare Gynemesh

[133] ETH.MESH.02282833: Email series 07 Oct 2004, Subject: TVM – First training – key learnings.

[134] *Id.*

[135] *Id.*

[136] *Id.*

[137] ETH.MESH.02282833-834: Email series 07 Oct 2004, Subject: TVM – First training – key learnings.

[138] ETH.MESH.02282833 at 834: Email series 07 Oct 2004, Subject: TVM – First training – key learnings. * Trademark

[139] *Id.*

[140] ETH-03532-533: February 28, 2005, Summary Memo for Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA) with accompanying Revision C DDSA.

[141] ETH-03533 at 536: February 25, 2005, Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA).

question "Have safety or efficacy issues occurred in the use of predicate, or other similar, devices?" that there are "**No known predicate/similar devices**."[142] (Emphasis added.) The affirmative response to the question "Is the user likely to use the device in a manner other than that described in the Instructions for Use?" substantiates that "Ramifications could range from device failure to patient harm as identified in Appendix VI of this document."[143] It is further noted in Appendix X of the DDSA, regarding whether "Long-term use of equivalent product has been considered from both the positive and negative perspective," e.g., "Clinical/Scientific reports, both internal and published" and "Device failure reports," that "**Currently there is no equivalent product indicated for this procedure.**" (Emphasis added.)[144]

5) Further, the "Qualitative & Quantitative Characteristics Worksheet" of the final DDSA documents new issues of safety and effectiveness that were not present with the GYNEMESH device. Special training of the intended user is needed[145] and the device utilizes invasive contact with the patient in terms of not only the mesh but also the three instruments (guide, cannula, retrieval line).[146] By the time of this final DDSA (February 25, 2005), Ethicon knew the difficulties for even highly skilled surgeons to learn the novel TVM Prosthetic Repair Technique. Moreover, the Design Validation Report for the PROLIFT, dated February 7, 2005, documented that "Clearly for most physicians the PROLIFT procedure will be a deviation from what they are currently doing."[147]

6) The PROLIFT Instructions for Use (IFU) referred the user to "the recommended surgical technique for the GYNECARE PROLIFT* Pelvic Floor Repair Systems for further information on the GYNECARE PROLIFT procedures"[148] and provided instructions for using the PROLIFT device in a different fashion from that originally cleared for the GYNEMESH product. FDA views such labeling changes as having the potential to affect safety and/or effectiveness and as major changes in intended use that require submission of a 510(k).[149]

In my professional opinion, these multiple examples affirmatively establish, beyond any doubt, that the changes in the PROLIFT device as compared to the GYNEMESH device posed the potential to significantly impact safety and effectiveness and, therefore, Ethicon was required, at a minimum, to submit a 510(k) premarket notification and receive 510(k) clearance prior to marketing the PROLIFT. My opinion is consistent with FDA's determination in August 2007 that a 510(k) submission and 510(k) clearance were required prior to marketing the device. Ethicon failed to comply with the standard of care required of a reasonably prudent medical device

[142] ETH-03533 at 550: February 25, 2005, Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA), Appendix IV "Use Related Hazard Worksheet."
[143] *Id.*
[144] ETH-03533 at 565: February 25, 2005, Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA), Appendix X, DDSA Activity Form.
[145] ETH-03533 at 537: February 25, 2005, Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA), Appendix III, Qualitative & Quantitative Characteristics Worksheet.
[146] ETH-03533 at 538: February 25, 2005, Revision C of the Gynecare PROLIFT Device Design Safety Assessment (DDSA), Appendix III, Qualitative & Quantitative Characteristics Worksheet.
[147] ETH.MESH.00020625 at 630: Design Validation Report, GYNECARE PROLIFT Pelvic Floor Repair System, Section 4.2, Product Evaluation Results – Below Average Evaluations and Associated Comments (included in AddTo-File for K013718, beginning at ETH.MESH.00020394).
[148] ETH.MESH.00521967 (also ETH-10286): Gynecare PROLIFT Instructions for Use.
[149] *Draft* Guidance for Industry and FDA Staff – 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device, Issued July 27, 2011.

manufacturer in its decision to proceed with marketing the PROLIFT without submitting a 510(k). Importantly, Ethicon could have sought guidance from FDA to determine the appropriate regulatory pathway. As Ethicon itself admitted, applicable regulations require 510(k) clearance prior to marketing of any change to an existing device that has the capacity to raise new issues of safety and effectiveness.[150]

Further, devices for which there is no legally marketed predicate device, as was documented in the PROLIFT DDSA, are automatically considered Class III (high risk devices) and require a PMA prior to marketing. Alternatively, the manufacturer may request reclassification, submit a request for evaluation of the automatic Class III designation, or present new evidence (data) to support a 510(k) clearance.

D. Re-Evaluation of Regulatory Strategy for PROLIFT Post Market Launch

"During April 23-26, 2007, the FDA conducted an audit of Ethicon's Norderstedt, Germany manufacturing facility. The FDA auditor requested Ethicon to submit a new 510(k) for the currently marketed Ultra Pro Hernia System after review of the Regulatory Strategy and the decision not to file a new 510(k) before marketing the Ultra Pro Hernia System line extension."[151] This request by the FDA auditor triggered an updated strategy review of Ethicon's similar decision (2003-2005) that the PROLIFT did not require a 510(k) submission to FDA.

This 2007 updated review yielded the same decision as the original regulatory strategy determination, i.e., that a 510(k) for PROLIFT was not required.

E. Submission of 510(k) Premarket Notification for PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems: K071512

On June 1, 2007, Ethicon submitted a traditional 510(k) Premarket Notification to FDA for the GYNECARE PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems (PROLIFT+M).[152] In contrast to the PROLIFT device for which the mesh is nonabsorbable PROLENE soft (polypropylene) mesh, the PROLIFT+M is based on modifications to ULTRAPRO mesh and provides a partially absorbable mesh for "tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect."[153] According to the testimony of Dr. David Robinson, the PROLIFT+M was developed as a "design improvement" of the PROLIFT and, in particular, "to minimize the mesh load given to the patient and increase the flexibility of the mesh that was being used in the pelvis," with the expectation that this would benefit the patient, both from a safety and effectiveness standpoint.[154]

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[150] Catherine Beath deposition, 3/27/12, 483:14 - 485:14.
[151] ETH.MESH.00011731: Regulatory Strategy Review, GyneCare Prolift Pelvic Floor Repair System (Project D'Art), 6/13/2007.
[152] ETH.MESH.00748571 at 582: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Cover Letter.
[153] ETH.MESH.00748571 at 586: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Indications for Use.
[154] David Robinson deposition transcript (rough draft), 3/14/12: 15:7-20, 24-16:13.

The PROLIFT+M "mesh implant is constructed of knitted filaments of equal parts of absorbable poliglecaprone-25 monofilament fiber and nonabsorbable polypropylene monofilament fiber, **which is identical in composition to the currently marketed ULTRAPRO mesh (K03337) [sic] (ETHICON, Inc).**"[155] The other components of the PROLIFT+M are the three instruments, i.e., the guide, cannula, and retrieval device, used for the PROLIFT.[156]

In this 510(k) for PROLIFT+M, the PROLIFT was identified as a predicate device and "insignificant change – line extension of GYNECARE GYNEMESH PROLENE Soft Mesh – K013718, product code FTL," and, "therefore, no Premarket Notification was necessary. The PROLIFT Systems consisted of a shape change to the currently marketed GYNECARE GYNEMESH PS as well as the addition of inserter tools to create a procedural kit."[157] It is notable, however, that the PROLIFT+M 510(k) reports that "Arm pulloff testing is conducted to ensure that the mesh implants can withstand the forces applied during a PROLIFT procedure. Prior testing determined the force required to pull a GYNECARE GYNEMESH M mesh implant arm through the PROLIFT cannula to be 0.73 lbf. Based on this data and the data collected during performance testing, it can be concluded that the GYNEMESH M mesh implant has adequate strength to withstand the forces applied during a PROLIFT placement."[158] This testing further substantiates that the shape changes to GYNEMESH for the design of the original PROLIFT mesh posed the potential to affect safety and/or effectiveness, and, accordingly, Ethicon was required to submit a 510(k) prior to marketing the PROLIFT. Scott Jones, Ethicon's marketing designee, testified how Ethicon defines line extension from a marketing perspective and in so doing acknowledged that PROLIFT is not simply a line extension of the Gynemesh rectangle.[159]

F. Rationale and Summary Submitted to FDA for the "Insignificant Change" from GYNEMESH PS to the PROLIFT Device: K071512 S01

Pursuant to a telephone call with Dr. Jiyoung Dang, Biomedical Engineer, FDA, on July 19, 2007, Bryan Lisa, Regulatory Affairs Project Manager, provided FDA with a rationale and summary for the "insignificant change" from GYNEMESH PS to the PROLIFT device. Mr. Lisa discussed that the PROLIFT was considered to be a line extension of GYNEMESH (K013718) and, therefore, legally marketable. The PROLIFT Systems consisted of "a shape change to the currently marketed GYNECARE GYNEMESH PS as well as the addition of inserter tools to create a procedural kit. GYNECARE PROLIFT is provided pre-shaped to the surgeon as a matter of convenience." Based on these changes, "it was deemed that no Premarket Notification was necessary for GYNECARE PROLIFT Pelvic Floor Repair Systems."[160]

In response, Dr. Dang advised Mr. Lisa that she had spoken with the branch chief regarding the changes made to the GYNEMESH device cleared under K013718, and the changes made required

[155] ETH.MESH.00748571 at 596: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Executive Summary.
[156] ETH.MESH.00748571 at 617: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Substantial Equivalence - Predicate Devices.
[157] ETH.MESH.00748571 at 617: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Substantial Equivalence - Predicate Devices.
[158] ETH.MESH.00748571 at 619: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Substantial Equivalence - Discussion of Similarities and Differences.
[159] Scott Jones deposition, 1/25/12, 912:16-913:24.
[160] ETH.MESH.00020389: Telephone Call Record, 7/19/07, Jiyoung Dang, FDA, and Bryan Lisa, Ethicon RE: K071512 S01 – Rationale for Insignificant Change to GYNEMESH PS.

at minimum for Ethicon to submit an Add-to-File to be included in the K013718 records. The Add-to-File should include the specific changes made, a statement of whether or not the changes altered the safety and effectiveness of the product as compared to the device cleared under K013718, and any and all relevant tests and data related to the performance of the new, altered device, i.e., the PROLIFT System.[161]

G. Add-To-File for K013718 (GYNECARE GYNEMESH PS Nonabsorbable PROLENE Soft Mesh) Submitted to FDA and Converted to 510(k)

Ethicon submitted the Add-To-File requested by FDA on August 6, 2007.[162] Three days later Dr. Dang requested a better quality copy of the data for the gas chromatography and HPLC assays, which was provided to FDA on the same day.[163] The following day, August 10, 2007, Dr. Dang advised Mr. Lisa that FDA had "determined that the shape changes made to the originally cleared Gynemesh are significant [sic] and did require the submission of a 510(k)." FDA further advised that, rather than request Ethicon to submit a new 510(k), the Agency would include the Add-To-File as an amendment to the PROLIFT+M 510(k) (K071512/A01) and would review the information as part of K071512.[164] Ethicon was, therefore, on notice that the company was marketing the PROLIFT without a requisite 510(k).

H. FDA Requests Ethicon to Address Multiple Deficiencies and Advises that the Device May Not Be Marketed Until Deficiencies Are Resolved and Ethicon Receives FDA Letter Authorizing Marketing

Subsequent to FDA's review of the original 510(k) submission (K071512) and the Add-To-File incorporated into the submission, Ethicon received a letter signed by David Krause for Mark Melkerson, Director, Division of General, Restorative and Neurological Devices, Office of Device Evaluation, CDRH, dated August 24, 2007, which requested Ethicon to address multiple (16) deficiencies in order for the Agency to complete review of the submission. Among these, FDA asked Ethicon to provide a rationale for substantial equivalence of the PROLIFT and PROLIFT+M Systems to the predicate devices, stating that the unique shapes of the meshes in the PROLIFT Systems are significantly different from previously cleared rectangular meshes and "have the potential to raise new questions of safety and effectiveness given that surgical procedure using the Prolift Systems will not be equivalent to the surgical procedure for placement of the predicate devices."[165] Since PROLIFT (originally listed as a predicate device for the PROLIFT+M) was now a candidate device for 510(k) clearance (K071512), the two remaining predicate devices were the ULTRAPRO mesh (K033337) and GYNECARE GYNEMESH PROLENE Soft (polypropylene) Nonabsorbable Synthetic Surgical Mesh (K013718).[166]

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[161] ETH.MESH.00020392: Email 7/31/07, Jiyoung Dang, FDA, to Bryan Lisa, Ethicon RE: K071512 S01 – Follow up.
[162] ETH.MESH.00020394: Cover Letter, Add-To-File, August 6, 2007.
[163] ETH.MESH.00372319: Email series, August 9, 2007, between Jiyoung Dang, FDA, and Bryan Lisa, Ethicon.
[164] ETH.MESH.00080934: Email, August 10, 2007, Jiyoung Dang, FDA, to Bryan Lisa, Ethicon.
[165] ETH.MESH.00372330: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[166] ETH.MESH.00748571 at 617: Traditional 510(k) Premarket Notification - PROLIFT+M Pelvic Floor Repair Systems, Substantial Equivalence - Predicate Devices.

Almost half of FDA's listed deficiencies were related to clinical evaluation and use concerns. FDA asked for clarification regarding whether any clinical studies had been conducted with either the PROLIFT or PROLIFT+M and requested complete study reports for any study(ies) done.[167] FDA asked for justification of Ethicon's conclusion that clinical evaluation of the meshes was not necessary, citing cautionary remarks in a publication in the 510(k) submission concerning the use of biomaterials in pelvic surgery because of the mesh size and resultant increased biomaterial load.[168] Moreover, FDA advised that a significant number of adverse events had been reported to the Agency both for the TVT device and also the GYNEMESH device, identical in composition and intended use to the PROLIFT System. Accordingly, FDA requested discussion concerning how the PROLIFT System can be used safely and effectively, "taking into account these reported adverse events."[169]

FDA specifically requested Ethicon to provide a clinical evaluation of the "proposed Prolift System" to support the Indications for Use, stating that "bench testing is not sufficient to demonstrate device safety and efficacy" due to the complex procedure proposed to be done in a "blind" manner using specialized surgical tools and a "potential high risk for organ perforation." Similarly for the PROLIFT+M System, FDA requested Ethicon to provide a clinical evaluation, because the tests provided "do not support the successful use of the Prolift+M System for a complicated surgical procedure and placement of this device." Specifically, the biocompatibility, bench performance, and animal testing provided were for the ULTRA PRO mesh "intended for use in hernia repair which is significantly different in anatomical location and pathology than pelvic floor and vaginal wall prolapse repair" and, therefore, insufficient "to support the use of a partially absorbable mesh for pelvic floor and vaginal wall prolapse repair."[170]

FDA was also concerned about the surgical training required to learn how to use the PROLIFT and PROLIFT+M Systems. Based on "obvious usage differences between inexperienced and experienced physicians" who evaluated the PROLIFT and PROLIFT+M Systems, respectively, in a cadaver, FDA requested a description of the training requirements, including the duration and intensity of training, "in order to have a successful surgery with minimal errors with the physician's first patient."[171]

Among the other deficiencies FDA identified were questions related to technological and performance characteristics, labeling issues, and the need to submit the several essential items required in a 510(k) that were missing due to the conversion of the Add-To-File for PROLIFT to a 510(k) submission, e.g., labeling, revised Indications for Use, Truthful and Accurate Statement, and 510(k) Summary, including a detailed and comprehensive description of material components and performance testing.[172]

Significantly, FDA advised Ethicon that "You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (ACT)."

[167] ETH.MESH.00372330: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[168] ETH.MESH.00372330 at 331: *Id.*
[169] *Id.*
[170] ETH.MESH.00372330 at 332: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[171] ETH.MESH.00372330 at 333: *Id.*
[172] ETH.MESH.00372330 at 332-333: *Id.*

Further, FDA advised, "You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations."[173] In disregard of FDA's directive and in violation of the ACT, Ethicon continued to market the PROLIFT.

I. Ethicon's Responses to FDA-Identified Deficiencies (K071512 S02 and S03)

On September 20, 2007, Ethicon submitted its response (K071512 – S02) to the deficiencies listed in FDA's August 24, 2007, letter.[174] The response was supplemented on October 15, 2007, with K071512 S03, which provided "data to exhibit the effects of the relaxation and laser cutting operations to ULTRAPRO mesh to create the mesh implant for the PROLIFT+M Pelvic Floor Repair Systems."[175]

To address FDA's request for a rationale for substantial equivalence of the PROLIFT and PROLIFT+M to the ULTRAPRO and GYNEMESH devices, Ethicon amended its predicate devices for K071512 to include the Apogee Vault Suspension System and the Perigee System, claiming substantial equivalence based on shape, insertion procedure, and performance characteristics, and noting that both systems "require 'blind' passage of surgical instruments in the vaginal wall, similar to the PROLIFT and PROLIFT+M systems."[176] (Note that in this submission, Ethicon identified the inserter tools as Class I devices, if sold separately, classified under regulation 21 CFR § 878.4800.) Further, stating that "we do not feel that clinical studies are necessary to demonstrate substantial equivalence," Ethicon provided the TVM internal study reports to FDA, characterizing these studies as post-market clinical evaluations "with the purpose of evaluating the GYNEMESH for anterior, posterior and vault prolapse repair using the TVM technique. These samples were provided pre-cut, in shapes similar to the GYNECARE PROLIFT system with a single, simple insertion instrument, but were not provided with a complete set of inserter tools. Therefore, no clinical investigations were conducted on the use of GYNECARE PROLIFT Pelvic Floor Repair System."[177] While Ethicon characterized the TVM studies as post-market evaluations of GYNEMESH, in fact, these were feasibility studies of the TVM technique for genital prolapse.[178,179] Additionally, according to Dr. David Robinson's testimony, while the product used in the TVM studies wasn't the exact PROLIFT kit, "We considered it an accurate representation thereof."[180]

In response to FDA's inquiry concerning how the PROLIFT can be used safely and effectively, considering the number of complaints and MDRs reported to FDA for GYNEMESH, Ethicon compared adverse event rates for GYNEMESH and PROLIFT and concluded that MDR rates (number reported/sales) were comparable for the time period evaluated (2005 through 2007 YTD). Further, Ethicon reported to FDA that "Through Design Validation and cadaver modeling, GYNECARE PROLIFT and GYNECARE PROLIFT+M have been shown to not introduce new issues of safety and efficacy from the predicate, GYNECARE GYNEMESH."[181]

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[173] ETH.MESH.00372330 at 334: *Id.*
[174] ETH.MESH.00372336: Email, September 20, 2007, from Bryan Lisa to Jiyoung Dang, FDA, RE: K071512 – S02.
[175] ETH.MESH.00372640: Ethicon's K071512 S03 submission to FDA, 10/15/07.
[176] ETH.MESH.00372341 at 342: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[177] *Id.*
[178] ETH.MESH.00357123: Clinical Study Report, Protocol Number CT-TVM-001-03, 27 June 2006.
[179] ETH.MESH.00357204: Clinical Study Report, Protocol Number 2003-016, 28 June 2006.
[180] Dr. David Robinson deposition, 3/14/2012, 338:23-339:7
[181] ETH.MESH.00372341 at 344-345: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.

However, Ethicon did not disclose to FDA that clinical experience with PROLIFT had led Ethicon to a decision to reengineer PROLIFT, which resulted in the development of PROLIFT+M.[182] Specifically, "The Prolift+M® was designed in a response to minimize the mesh load given to the patient and increase the flexibility of the mesh that was being used in the pelvis," with the desire that this would benefit the patient, both from a safety and efficacy standpoint.[183] Ethicon also did not disclose to the FDA that by November 2005, it was known within Ethicon that the PROLIFT was going to be changed in certain ways[184] and, notably, that Dr. Jacob Eberhard, a European (Switzerland) surgeon who had done over 70 PROLIFT surgeries, had brought a number of PROLIFT safety issues to the attention of Ethicon, namely, Axel Arnaud, Scientific Director, Gynecare Europe.[185] These included that the transgluteal approach with posterior trocar passes is too dangerous for the rectum, and he would not do that.[186] Dr. Eberhard believed there are too many steps needed to insert the PROLIFT straps, also that "The guide is too sharp" and "This is unnecessary and presents a risk for the vessel or bowel perforation."[187] Among other suggested modifications, "He believes that, after retrieval of the cannula, the straps take a rope-like shape which is not optimal in his opinion. He has observed that some patients have discomfort as they can feel the straps with Prolift."[188] Nor did Ethicon report to FDA that by November 24, 2006, it was known there were two issues with the PROLIFT from the perspective of some experts, including Professor Jacquetin, who created the PROLIFT product or was the leader of the team that created the product: erosions and shrinkage.[189] At this point, the erosion and shrinkage problems were significant enough that Ethicon was trying to find a way to address them.[190] According to Dr. Robinson's testimony, both the mesh and the surgical technique can be factors leading to erosion.[191] As regards shrinkage, it was believed the responsibility of the mesh was more established and "further to the expert's discussion, it was speculated that Ultrapro could be (not is) a solution for this problem, which is less common but can be more severe than erosion."[192] (Note that the mesh doesn't shrink but the problem is described as shrinkage.[193])

Further, Ethicon's response to FDA's request for a clinical evaluation of the proposed PROLIFT System, because of the complexity of the procedure and potential high risk for organ perforation, belied the information known to Ethicon at the time. Specifically, Ethicon responded that "Although the Design Validation report exhibits a mesh placement that may appear complex, the knowledge and dissection of these spaces are part of a gynecologist's training. Therefore, the anatomical region is not considered 'complex' to a trained gynecologist. For the GYNECARE PROLIFT System, cadaver modeling and Design Validation presented no issues of safety and efficacy in relation to user interface with the device. In addition, the Instructions for Use for PROLIFT and PROLIFT+M Systems state, '[t]raining on the use of the [Systems] is

[182] Dr. David Robinson deposition, 3/14/2012, 350:6-10.
[183] Dr. David Robinson deposition, 3/14/2012, 350:22-351:11.
[184] Dr. David Robinson deposition, 3/14/2012, 378:7-379:6.
[185] Dr. David Robinson deposition, 3/14/2012, 369:22-371:10; 374:10-18.
[186] Dr. David Robinson deposition, 3/14/2012, 371:11-20.
[187] Dr. David Robinson deposition, 3/14/2012, 371:22-372:16.
[188] Dr. David Robinson deposition, 3/14/2012, 373-915.
[189] Dr. David Robinson deposition, 3/14/2012, 447:10-448:15.
[190] Dr. David Robinson deposition, 3/14/2012, 451:17-24.
[191] Dr. David Robinson deposition, 3/14/2012, 449:20-24.
[192] Dr. David Robinson deposition, 3/14/2012, 450:19-451:16.
[193] Dr. David Robinson deposition, 3/14/2012, 448:22-449:1.

recommended and available. Contact your company sales representative to arrange for this training.'" Significantly, none of the clinical experience or modifications needed to the PROLIFT, discussed above in this section, were provided to FDA. Nor were the issues identified in the first TVM-Training course in October 2004 (some of which are restated below) provided to FDA:

- "It was shown that a key part of the training is in the 'Feel' of the needle passages to ensure they pass in the right place through the right structures. **Cadavers may not give this full experience** and where possible the training surgeons need to get hands on in live surgery by either 'scrubbing in' where allowed. Or by having the preceptor go to their institution to help guide the passage of the needles."[194] (Emphasis added.)
- "The dissection of the posterior compartment for this procedure is significantly different to that for either standard sacro-spinous fixation procedures (Richter) or for even Posterior IVS....It was considered **more technically challenging than they had thought**."[195] (Emphasis added.)
- "There is a wide range of opinion on how many cases will be needed for a preceptor to become sufficiently proficient to teach this procedure. **Anything from 5 cases to 3 months (30 cases) to assess the procedure and learn the tricks**."[196] (Emphasis added.)

Moreover, on June 30, 2006, Ethicon knew, based on a document entitled "Definition for MAJOR INVASIVE SURGERIES And The Ethicon Franchise Products Requiring Major Invasive Procedures for Implantation" that the PROLIFT required major invasive surgery for implantation.[197] Regardless of this and the above knowledge, Ethicon advised FDA "Ethicon believes that the results of pre-clinical, benchtop testing, and cadaver evaluations....demonstrate that surgeons can use the device without problems."[198]

Moreover, Ethicon confirmed to FDA that the following statement, for which Ethicon agreed that sufficient evidence had not been provided, had been removed from the IFU: "The bidirectional elastic property allows adaptation to various stresses encountered in the body."[199] However, the IFU dated 11/9/07 retained this statement.[200] This IFU was used from December 17, 2007, through September 24, 2009, fully two years beyond the time Ethicon confirmed to FDA that the statement had been removed.[201]

J. FDA Unable to Complete Review of 510(k) (K071512 S01) Because Ethicon Did Not Completely Respond to Deficiencies Listed in August 24, 2007, Letter

In a letter dated December 20, 2007, FDA advised Ethicon that a substantial equivalence decision could not be made because Ethicon did not completely respond to the deficiencies listed in FDA's August 24, 2007, letter. FDA listed the deficiencies that remained to be addressed in order for the Agency to complete review of the 510(k) and again advised Ethicon that "You may not market this

[194] *Id.*
[195] ETH.MESH.02282833-834: Email series 07 Oct 2004, Subject: TVM – First training – key learnings.
[196] ETH.MESH.02282833 at 834: Email series 07 Oct 2004, Subject: TVM – First training – key learnings.
[197] ETH.MESH.00329334 at 335-336: June 30, 2006, email from Meng Chen to Mark Yale RE: The feedback from the medical directors for the IFU updates.
[198] ETH.MESH.00372341 at 347: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[199] ETH.MESH.00372341 at 351: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[200] ETH.MESH.02341454 at 455: Gynecare PROLIFT Instructions for Use (IFU) dated 11/9/07.
[201] (No Bates Number) IFU Index and Production Bates Range Chart.

device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (ACT)." Further, FDA advised, "You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations."[202]

A teleconference was arranged for January 22, 2008, to discuss the deficiencies listed in the December 20, 2007, letter, including labeling for PROLIFT and PROLIFT+M, patient labeling, and FDA's request for financial disclosure information for the TVM study.[203] FDA's key concerns were related to revising the labeling to include clinical data from the TVM studies and adequately addressing issues of usability and potential adverse events in the labeling. Further, FDA requested Ethicon to "develop a Patient Brochure (patient labeling) to be provided when counseling a patient regarding options for treating pelvic organ prolapse."[204]

Resolution or a plan for resolution of remaining deficiencies was agreed during the teleconference. Bryan Lisa, Project Manager, Regulatory Affairs, Ethicon, again told FDA that the PROLIFT IFU "will be updated to remove the 'bi-directional elasticity' statement..."[205]

Dr. Krause, Chief, PRSB, FDA, advised Ethicon that "a PMI action team has been formed to deal with the adverse events associated with pelvic floor repair meshes," and "the PROLIFT+M submission is the first submission since the PMI action team was formed."[206] Although Jennifer Paine, Director, Regulatory Affairs, Ethicon, addressed FDA's request to add the following statement to the IFU, indicating it would put Ethicon at a disadvantage from competitive devices, Dr. Corrado, Medical Officer, OGDB, FDA, "stated that this IFU information will be enforced for devices of this nature in the future," and "D. Krause indicated that these changes are 'across the board'":[207] "The safety and effectiveness of synthetic mesh or film support in transvaginal surgical procedures to treat pelvic organ prolapse have not been demonstrated in prospective, randomized clinical trials."[208]

K. Ethicon Advised that NSE Letter Issued if Unresolved Deficiencies Exist after Response to Second AI Request

Following the January 22, 2008, teleconference, on February 7, 2008, Ethicon submitted a partial response to FDA's letter dated 12/20/07, noting that the response was expected to be completed in mid-February.[209] Dr. Dang replied, advising Mr. Lisa that "K071512 has already been placed on hold twice. Because of this, after review of your latest response to our last deficiency letter, I will need to make a final recommendation on the document." Dr. Dang further advised, "In general, if unresolved deficiencies exist following FDA's review of a response to a second AI

[202] *ETH.MESH.00372653 at 658: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.*
[203] ETH.MESH.00081347: 1/22/08 Teleconference information, from B. Lisa, Ethicon, to J.Dang, FDA.
[204] ETH.MESH.00372653 at 656: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[205] ETH.MESH.00372662: 1/22/08 Meeting Minutes (via Teleconference) RE: Discussion of AI Letter (K071512).
[206] *Id.*
[207] ETH.MESH.00372662-663: *Id.*
[208] ETH.MESH.00372653 at 655-656: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[209] ETH.MESH.00081420-421: February 7, 2008, Email with attachment, B. Lisa, Ethicon, to J. Dang, FDA, RE: K071512 S04.

request, FDA will issue a NSE letter." Dr. Dang recommended that Ethicon not send in a partial response.[210]

Jennifer Paine replied to Dr. Dang and asked that the electronic copy of the partial response be disregarded, stating that Ethicon "will plan to submit the complete response in the next two weeks."[211] Ethicon subsequently spoke with Dr. Krause to discuss whether Ethicon should withdraw the submission, due to concern about the risk of a NSE letter. Dr. Dang responded that, given the discussion during the recent teleconference, she believed the risk of a NSE decision was low and indicated the Agency "will try our best to work with you over the review of this latest supplement."[212]

L. Ethicon Submits Response on February 21, 2008, to Deficiencies Listed in December 20, 2007, Letter and Receives 510(k) Clearance on May 15, 2008

On February 21, 2008, Ethicon submitted its complete response to the deficiencies FDA listed in its letter of December 20, 2007. On May 5, 2008, Ethicon was notified of remaining deficiencies with the physician and patient labeling, which were necessary to be resolved before Dr. Dang could make a final recommendation for the premarket notification. Dr. Dang advised that "The labeling changes that have been and are being requested are labeling changes that are being requested during review of premarket notifications for mesh indicated for use in treatment of pelvic organ prolapse. This is part of an ongoing process to provide more accurate and informative labeling to both physicians and patients in response to an increase in receipt of adverse event reports related to the use of large, specially shaped mesh with the use of surgical tools to facilitate placement in a 'blinded' procedure for the treatment of pelvic organ prolapse."[213]

Notably, FDA remained firm that Ethicon must include the statement in the IFU that "The safety and effectiveness of this mesh compared to conventional surgical repair for pelvic organ prolapse have not been demonstrated in randomized controlled clinical trials." While the language FDA proposed also included Ethicon's suggested wording, "In the United States, substantial equivalence of Gynecare Prolift Pelvic Floor Repair Systems to synthetic mesh with the same indication has been demonstrated through benchtop and cadaveric testing," FDA did not accept the latter statement to stand alone. Dr. Dang explained that the Agency's "request was made due to the lack of evidence of the safety and effectiveness for transvaginal/transobturator/etc. placement of large, specially shaped mesh with the use of surgical tools to facilitate placement in a 'blinded' procedure for the treatement [sic] of pelvic organ prolapse through study in controlled, prospective, randomized clinical trials."[214]

Additionally, FDA requested revisions to the patient labeling, including among other changes, to advise patients that synthetic mesh is a permanent implant, that "[t]here are not enough data from clinical studies to know whether the benefits of this implant is [sic] greater than the risks, and to

[210] ETH.MESH.00081420: February 7, 2008, Email, J. Dang, FDA, to B. Lisa, Ethicon, RE: K071512 S04.
[211] ETH.MESH.00081418: Email 07 Feb 2008, J. Paine, Ethicon, to J. Dang, FDA, RE: K071512 S04.
[212] ETH.MESH.00081410-411: Email series 11 Feb 2008, B. Lisa, Ethicon, and J. Dang, FDA, RE: K071512 – response.
[213] 210 ETH.MESH.00081484: Email 05 May 2008, J. Dang, FDA, to B.Lisa, Ethicon, RE: Remaining deficiencies with K071512-Supplement 02 – Ethicon Prolift and Prolift+M.
[214] *Id.*

advise patients "that one of the most common adverse events is mesh extrusion and this complication usually requires the removal of the mesh and may interfere with sexual function."[215]

Ethicon responded on May 9, 2008, generally agreeing to FDA's requests, except that Ethicon did disagree with FDA that "the data (preclinical and clinical) available are insufficient to determine whether the benefits of the device are greater than the risks." Ethicon referenced the Clinical Expert Report that was the basis for CE-marking and proposed the following amended statement: "Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition."[216]

Ethicon received 510(k) clearance for Gynecare Prolift and Gynecare Prolift+M Total, Anterior, and Posterior Pelvic Floor Repair Systems on May 15, 2008.[217] The PROLIFT 510(k)-cleared Indications for Use are shown below:

> The GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems are indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.[218]

OPINION #1: Ethicon Marketed a Misbranded and Adulterated PROLIFT Device

The FDCA requires that a medical device be 510(k)-cleared[219] or approved[220] by FDA prior to introduction of the device into interstate commerce, except when a change made to an existing 510(k)-cleared device does not pose the potential to significantly affect the safety or effectiveness of the device or the intended use of the device.[221] For a device with an existing 510(k) clearance, a new 510(k) is required if the device is about to be significantly changed or modified in design, components, method of manufacture, or intended use.[222] The consequences of a failure to submit a necessary 510(k) for a change to a device are the same as those for failing to make any necessary 510(k) submission.[223] The FDCA prohibits the introduction into interstate commerce of adulterated or misbranded devices[224] and sets forth the circumstances in which a device would be adulterated[225] or misbranded.[226] The lack of a necessary 510(k) renders a device misbranded.[227] Lack of a necessary PMA renders a device adulterated.[228]

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[215] ETH.MESH.00081484-485: *Id.*
[216] 213 ETH.MESH.00748459 at 461-462: May 9, 2008, Response to FDA Letter on K071512: PROLIFT and PROLIFT+M Systems.
[217] ETH.MESH.00372780: K071512 Substantially Equivalent Letter.
[218] ETH.MESH.00372780 at 782: K071512 Substantially Equivalent Letter, Indications for Use.
[219] FDCA §§ 510(k), 513(i).
[220] FDCA § 515.
[221] 21 CFR § 807.81(a)(3).
[222] *Id.*
[223] Autor DM. Medical Device Law – An Overview. *Civil Resource Manual* 110, May 1996.
[224] FDCA §§ 301(a) and (c)
[225] FDCA § 501, 21 U.S.C. § 351.
[226] FDCA § 502, 21 U.S.C. § 352.
[227] FDCA §§ 301(p), 502(o), 21 U.S.C. §§ 331(p), 352(o).
[228] FDCA § 501(f), 21 U.S.C. § 351(f).

Based on my review and evaluation of the information discussed above in this Report, Ethicon deviated from the standard of care required of a medical device manufacturer by its failure to submit a 510(k) before marketing a new medical device or modified version requiring an additional clearance (a prohibited act).[229] Its failure to obtain a required 510(k) clearance rendered the PROLIFT misbranded.[230] Every new device that lacks a necessary 510(k) is considered to be a Class III device requiring a PMA by operation of law and, therefore, the PROLIFT was also adulterated.[231] In my professional opinion, Ethicon marketed a misbranded and adulterated PROLIFT device from the time of its product launch in early 2005 until 510(k) clearance was obtained.[232] Even thereafter, Ethicon continued to disseminate false and misleading information in the form of its IFUs, Patient Brochures and other marketing information with regards to the safety and effectiveness of the PROLIFT System.

OPINION #2: Ethicon Reported False and Misleading Information to FDA

During the review of the PROLIFT 510(k) (K071512/01), Ethicon failed to disclose to FDA known safety issues with the PROLIFT, as discussed above. Not only did Ethicon not disclose safety issues but Ethicon also reported to FDA that the PROLIFT did not introduce any new issues of safety or effectiveness as compared to the GYNEMESH predicate and "that surgeons can use the device without problems."[233] In my professional opinion, Ethicon submitted false and misleading information to FDA, in violation of the standard of care required of a medical device manufacturer. Submission to FDA of any device-related report required by or under the FDCA that is false or misleading in any material respect is a prohibited act.[234] Knowingly and willfully falsifying or concealing material facts or making any false statement to FDA is prohibited.[235]

As a consequence of Ethicon's actions, FDA relied on information that was materially inaccurate for its decision-making and ultimate clearance of the PROLIFT 510(k), which disrupted the regulatory process for which the purpose is to protect the public health. It is my professional opinion, based on my knowledge, training, and experience in medical product development, that FDA would not have cleared the PROLIFT for marketing without the clinical evaluation which it requested in its August 24, 2007, letter to Ethicon concerning 510(k) (K071512) deficiencies, had the Agency known of the adverse event and physician training issues discussed above.

[229] FDCA § 301(p), 21 U.S.C. § 331(p).
[230] FDCA § 502(o), 21 U.S.C. § 352(o).
[231] FDCA §§ 531(f)(1), 501(f)(1)(B)(i), 21 U.S.C. §§ 360c(f)(1), 351(f)(1)(B)(i).
[232] ETH.MESH.00748451: Substantial Equvalence Letter for Prolift and Prolift+M Total, Anterior, and Posterior Pelvic Floor Repair Systems, May 15, 2008.
[233] ETH.MESH.00372341 at 347: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[234] FDCA § 301(q)(2), 21 U.S.C. § 331(q)(2).
[235] 18 U.S.C. § 1001.

VI. MISBRANDING: INADEQUATE AND MISLEADING LABELING

A. PROLIFT Labeling Prior to and After 510(k) Clearance

Based on the "IFU Index and Production Bates Range Chart" provided by Ethicon's counsel, there have been four versions of the PROLIFT Instructions for Use (IFU), with the initial version used from January 11, 2005, through December 13, 2007, prior to 510(k) clearance (K071512) and during a part of the 510(k) (K071512) review process. The second version was in use from December 17, 2007, through September 24, 2009, i.e., during the 510(k) review process until 16½ months after 510(k) clearance. The first version reflecting the changes required by FDA for 510(k) clearance was first used 16½ months after 510(k) clearance on October 1, 2009, and continued in use through May 7, 2010. The current IFU was first used on May 11, 2010.

Most of the issues that FDA identified during its review of the proposed labeling submitted in the 510(k), i.e., the second IFU version, are equally applicable to the initial IFU. For example, according to the testimony of Dr. David Robinson, chronic pain and dyspareunia were known complications "from the start."[236] Yet these were not included under the "Adverse Reactions" in the IFU. Moreover, Axel Arnaud in January 2005 proposed to add the following to the IFU: "WARNING: Early clinical experience has shown that the use of mesh through a vaginal approach can occasionally/uncommonly lead to complications such as vaginal erosion and retraction which can result in an anatomical distortion of the vaginal cavity that can interfere with sexual intercourse. Clinical data suggest the risk of such a complication is increased in case of associated hysterectomy. This must be taken in consideration when the procedure is planned in a sexually active woman."[237] Yet, Sean O'Bryan advised that "The PROLIFT IFU ... most likely has gone out for translations and final proof so unless it is absolutely [sic] necessary we should leave it as is."[238] And Scott Ciarrocca replied, "We have already printed launch stock. This would be a 'next-rev' addition but they want it in there ASAP."[239] Such concerns should not delay implementation of IFU changes containing important safety information and override a manufacturer's compliance with the required standard of care.

The deficiencies in the multiple PROLIFT IFUs are discussed in detail below.

1. "Bi-directional" Statement Remains in Label for 2 Years after Ethicon Advised FDA It Was Removed

During the review of the proposed labeling submitted in the 510(k) (K071512), FDA advised Ethicon in a letter dated August 24, 2007[240] (and in an email dated August 27, 2007[241]), that

"You have not provided sufficient evidence to support the statement 'the bi-directional elastic property allows adaptation to various stresses encountered in the body.'" Ethicon was requested

[236] Dr. David Robinson deposition, 3/13/2012, 311:2-312:12.
[237] ETH.MESH.02286052 at 053: Email series January 11-13, 2005, RE: IFU Prolift.
[238] ETH.MESH.02286052: Email series January 11-13, 2005, RE: IFU Prolift.
[239] *Id.*
[240] ETH.MESH.00372330 at 333: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[241] ETH.MESH.00081118: Email, 21 Aug 2007, from Jiyoung Dang to Bryan, Lisa RE: K071512 – AI letter.

either to remove the statement from the Instructions for Use or "provide *in vivo* experimental evidence" demonstrating the "mesh has elastic properties that allows adaptation to physiological stresses."[242] Ethicon reported to FDA in its September 20, 2007, response, that "We agree that sufficient evidence has not been provided to make this statement. We have removed the statement from the IFU."[243] On January 22, 2008, Bryan Lisa, Project Manager, Regulatory Affairs, Ethicon, again told FDA that the PROLIFT IFU "will be updated to remove the 'bidirectional elasticity' statement..."[244] And once again in Ethicon's response to FDA on February 21, 2008, Mr. Lisa confirmed the "bi-directional" statement had been removed.[245] However, as discussed previously in this report, the IFU dated 11/9/07 retained this statement.[246] This IFU was used from December 17, 2007, through September 24, 2009, fully two years beyond the time Ethicon initially confirmed to FDA that the statement had been removed.[247]

2. ***Clinical and Safety Information to be Included in IFU per FDA's Request Not Implemented for 16½ Months After 510(k) Clearance***

In FDA's December 20, 2007, letter to Ethicon (discussed earlier in this report), FDA listed a number of deficiencies which Ethicon was required to address in order for FDA to render a substantially equivalent decision. A number of those deficiencies involved labeling issues. Notably, FDA advised Ethicon that the draft Instructions for Use (IFU) "do not adequately address issues of usability and potential adverse events," and labeling revisions were requested based on information from three sources: 1) data reported in the Trans-Vaginal Mesh (TVM) placement clinical evaluations (both European and U.S. cohorts); 2) analysis of adverse events reported to the FDA for the PROLIFT device; and 3) conclusions from publications specifically addressing PROLIFT device use.[248] Adverse reactions, contraindications, warnings, physician training, and summaries of the TVM placement clinical evaluations were among the information that was to be revised or added for the PROLIFT IFU, as discussed further below. Ethicon also was instructed that these sections of the IFU should be written in prominent text and placed before the section illustrating the recommended surgical technique.

2.1 Adverse Reactions

FDA provided Ethicon with a list of adverse events to be included in the IFU in its December 20, 2007, letter to Ethicon concerning deficiencies in the PROLIFT 510(k) (K071512/01).[249] Ethicon advised FDA on February 21, 2008, in its response to that letter, that the PROLIFT IFU had been updated to include the following adverse reactions (some of which Ethicon noted were already listed in the proposed labeling), in accordance with FDA's request:[250]

[242] ETH.MESH.00372330 at 333: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[243] ETH.MESH.00356982 at 992: Ethicon's K071512 S02 Submission to FDA, 9/20/07.
[244] ETH.MESH.00372662: 1/22/08 Meeting Minutes (via Teleconference) RE: Discussion of AI Letter (K071512).
[245] ETH.MESH.00372664 at 668: 2/21/08 Response to FDA's 12/20/07 Letter RE: K071512 S04.
[246] ETH.MESH.02341454 at 455: Gynecare PROLIFT Instructions for Use (IFU) dated 11/9/07.
[247] (No Bates Number) IFU Index and Production Bates Range Chart.
[248] ETH.MESH.00372653 at 655: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[249] ETH.MESH.00372653 at 656: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[250] ETH.MESH.00372664 at 666: 2/21/08 Response to FDA's 12/20/07 Letter RE: K071512 S04.

- hematoma
- urinary incontinence
- urinary retention/obstruction
- void dysfunction
- pain
- infection
- adhesions
- wound dehiscence
- nerve damage
- recurrent prolapse
- contracture
- procedure failure.

Ethicon also provided the proposed IFU for FDA's review.[251] Yet review of the IFU that was in use from December 17, 2007 (prior to 510(k) clearance), through September 24, 2009, shows that none of the adverse events from the above list was included on the IFU, except for those that were already present in the initially proposed labeling, specifically, infection potentiation, adhesion formation, and scarring that results in implant contraction.[252] Not until October 2009, 16½ months after 510(k) clearance, did the multiple other adverse reactions appear on the PROLIFT IFU. Nor did the adverse reactions appear in the location and prominence on the IFU required by FDA until October 2009. The IFU used from October 1, 2009, through May 7, 2010, still did not include procedure failure in the adverse event listing,[253] nor did the subsequent IFU still in use at the time Ethicon announced that it would cease marketing of the PROLIFT System.[254]

2.2 Contraindications

The "Contraindications" included in the IFU dated 11/9/07 included the following:

> "When GYNECARE GYNEMESH PS mesh is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows."

This IFU was in use, as noted above, from December 17, 2007, through September 24, 2009. However, the IFU that Ethicon submitted to FDA to resolve 510(k) deficiencies prior to clearance of the PROLIFT for marketing included the following "Contraindications":

[251] ETH.MESH.00748515 at 518: GYNECARE PROLIFT Pelvic Floor System Proposed IFU, K071512 S04 - Attachment 1.
[252] ETH.MESH.02341454 at 459: Gynecare PROLIFT Instructions for Use (IFU) (in use 17 Dec 07 to 24 Sep 09 per IFU Index and Production Bates Range Chart).
[253] ETH.MESH.02341734 at 736: Gynecare PROLIFT Instructions for Use (IFU) (in use 1 Oct 09 to 7 May 10 per IFU Index and Production Bates Range Chart).
[254] ETH.MESH.02341658 at 660: Gynecare PROLIFT Instructions for Use (IFU), STATUS: 02/2010 (in use 11 May 2010 to present day per IFU Index and Production Bates Range Chart).

1. GYNECARE GYNEMESH PS Mesh should not be used in infants, children, pregnant women, or women planning future pregnancies, as the mesh will not stretch significantly as the patient grows.
2. GYNECARE GYNEMESH PS Mesh must always be separated from the abdominal cavity by peritoneum.
3. GYNECARE GYNEMESH PS Mesh must not be used following planned intraoperative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection that may require removal of the mesh.
4. The GYNECARE PROLIFT Systems should not be used in the presence of active or latent infections or cancers of the vagina, cervix, or uterus.

Contraindications #2. through #4. did not appear on the IFU until October 1, 2009. Nor did the contraindications appear in the location and prominence on the IFU required by FDA until October 2009.

Further, Ethicon had information that certain patient populations were more likely to experience negative outcomes as a result of the use of the PROLIFT System. Such information should have been included in the contraindications section of the PROLIFT IFU.[255] Dr. Hinoul, Ethicon's Medical Affairs designee, testified at the FDA Obstetrics and Gynecology Devices Advisory Committee meeting in September 2011 that certain patient populations were at higher risk for complications from the PROLIFT System and testified in his deposition that Ethicon was aware of this fact since the time of the PROLIFT launch.[256] Rather than put this information in the contraindications section (or anywhere else in the labeling materials), Ethicon instead stated the following: "Pelvic floor repair procedures with GYNECARE PROLIFT are appropriate for almost all patients, including overweight patients, elderly patients, and even those that have undergone previous operations for pelvic organ prolapse or stress incontinence."[257] Ethicon also stated that PROLIFT is likely to be a good choice for those who have a smoker's cough.[258]

2.3 Warnings

FDA requested Ethicon to "add a warning to your labeling to recommend that surgeons perform cytoscopy to confirm bladder integrity or to detect bladder perforation" in its December 20, 2007, letter of deficiencies in the PROLIFT 510(k).[259] Ethicon affirmed

[255] Catherine Beath deposition, 3/26/12, 114:2-115:12
[256] Piet Hinoul deposition 4/6/12, 480:8-480:20; Hinoul FDA Advisory Committee Testimony at pg 145 ("One of the most important questions we need to ask ourselves is also why these adverse events are occurring. And the risk factors for mesh exposures are becoming more and more apparent. Several studies published this year show that hysterectomy, patient age, smoking, diabetes, and surgeon experience predispose patients to mesh exposure. Patient selection and risk factors, appropriately stated in the device's labeling, as well as the surgeon's training, are therefore part of our proposal.")
[257] 254 ETH.MESH.03905968 at 974: Patient Brochure, copyright 2005, titled "Pelvic Organ Prolapse – Get the Facts, Be Informed, Make YOUR Best Decision," Approval Date: 11/9/2005 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[258] ETH.MESH.00033400; See also Plaintiff's Exhibit 241 at pg 71 which is Ethicon's website.
[259] ETH.MESH.00372653 at 656: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.

the IFU had been updated accordingly and, additionally, that Ethicon had added the following Warning: "A digital rectal exam should be performed to detect possible rectal perforation."[260] The final proposed IFU submitted to FDA prior to 510(k) clearance included these two additional Warnings plus the other Warnings and Precautions listed below as #9 through #18."[261]

However, review of the IFU that was in use from December 17, 2007 (prior to 510(k) clearance), through September 24, 2009, shows only the Warnings and Precautions (#1 through #8) below:

1. Users should be familiar with surgical procedures and techniques involving pelvic floor repair and nonabsorbable meshes before employing the GYNECARE PROLIFT Pelvic Floor Repair Systems.
2. Acceptable surgical practices should be followed in the presence of infected or contaminated wounds.
3. Post-operatively the patient should be advised to refrain from intercourse, heavy lifting and/or exercise (e.g., cycling, jogging) until the physician determines when it is suitable for the patient to return to her normal activities.
4. Avoid placing excessive tension on the mesh implant during handling.
5. Refer to the recommended surgical technique for the GYNECARE PROLIFT Pelvic Floor Repair System for further information on the GYNECARE PROLIFT procedures.
6. The GYNECARE PROLIFT Pelvic Floor Repair Systems should be used with care to avoid damage to vessels, nerves, bladder and bowel. Attention to patient anatomy and correct use of the device will minimize risks.
7. Transient leg pain may occur and can usually be managed with mild analgesics.
8. Do not manipulate the GYNECARE PROLIFT Retrieval Device with sharp instruments or cut it to alter its length.

The FDA-requested Warning recommending that surgeons perform cytoscopy to confirm bladder integrity or to detect bladder perforation did not appear on the IFU until October 1, 2009, 16½ months after 510(k) clearance. Nor did the Warning that Ethicon added to perform a digital rectal exam to detect possible rectal perforation, or the other Warnings and Precautions listed below, which were included in the final proposed labeling submitted to FDA, appear in PROLIFT labeling until October 2009 (Warnings and Precautions presented separately as shown):

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[260] ETH.MESH.00372664 at 666: 2/21/08 Response to FDA's 12/20/07 Letter RE: K071512 S04.
[261] ETH.MESH.00748459 at 469: May 9, 2008, Response to FDA Letter on K071512: PROLIFT and PROLIFT+M Systems.

Warnings

9. Patients on anticoagulation agents undergoing surgery using the GYNECARE PROLIFT System must have their anticoagulation therapy carefully managed.
10. Do not remove the GYNECARE PROLIFT Cannulas from the patient until the mesh implant has been properly positioned.

Precautions

11. Do not affix the GYNECARE GYNEMESH PS Mesh Implant with any staples, clips, or clamps as mechanical damage to the mesh may occur.
12. This product should only be used under the prescription of a physician.
13. In patients with compromised immune systems or other conditions that would compromise healing, the risks and benefits should be carefully weighed.
14. Vaginal or urinary tract infection should be treated and alleviated prior to implantation.
15. If the mesh implant is used in contaminated areas, it must only be with the understanding that subsequent infection may require its removal. (Note: this was added to a revision of #2 Warning above.)
16. Prolapse repair may unmask pre-existing incontinence conditions.
17. Prophylactic antibiotics can be administered according to the surgeon's usual practice.
18. The use of this product with tissue adhesives is not recommended, as data are not currently available.

(Note that Warning #5 was removed from "Warnings" and "Precautions" and included only as an instruction in the beginning of the IFU, preceding the statement of "Indications," in the IFU in use from October 1, 2009.)

As discussed previously for Adverse Reactions and Contraindications, the Warnings and Precautions did not appear in the location and prominence on the IFU required by FDA until October 2009.

The IFU for PROLIFT also included a "Performance" section which stated as follows:

> "Animal studies show that implantation of GYNECARE GYNEMESH PS mesh elicits a minimum to slight inflammatory reaction which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes."[262]

[262] ETH.MESH.02341454-459: Gynecare PROLIFT Instructions for Use (IFU) (in use 17 Dec 07 to 24 Sep 09 per IFU Index and Production Bates Range Chart).

Ethicon had information that the above statement was untrue as it relates to the PROLIFT. Specifically, the minutes of an Ethicon expert meeting on June 2, 2006, show that Ethicon was aware that fibrosis is responsible for complications in mesh usage and that mesh creates a foreign body reaction that is not transient but rather an active process, a "chronic wound" that contributes to mesh contraction.[263] Ethicon was also aware that the "scar plate that forms with in-growth of tissue into the mesh can cause stiffness of the vagina," which was contrary to any statement regarding the mesh remaining soft and pliable post implantation.[264]

2.4 Physician Training

FDA requested Ethicon, in its December 20, 2007, letter listing 510(k) deficiencies, to expand the statement in the IFU that recommends training in the use of surgical mesh for pelvic organ prolapse also to include training in the management of complications resulting from such procedures.[265] The statement submitted to FDA in the final proposed labeling prior to 510(k) clearance was the following: "Training on the use of the GYNECARE PROLIFTTM Pelvic Floor Repair Systems is recommended and available. Contact your company sales representative to arrange for this training. Physicians should have experience in management of complications resulting from procedures using surgical mesh."[266]

The IFU that was in use from December 17, 2007, through September 24, 2009, however, did not include the expanded statement regarding experience in management of complications. The statement in that IFU was as follows: "Training on the use of the GYNECARE PROLIFTTM Pelvic Floor Repair Systems is recommended and available. Contact your company sales representative to arrange for this training."[267] The expanded statement required by FDA did not appear in the labeling until October 1, 2009.[268]

2.5 Summary of Clinical Data

FDA believed it was important to include a summary of the clinical data from the TVM internal study reports (discussed previously) in the IFU, due to the serious nature of the Medical Device Reports associated with anterior/posterior vaginal wall repairs using GYNECARE GYNEMESH received by FDA.[269] Accordingly, FDA requested Ethicon to include a summary of the clinical data and provide the revised labeling for the Agency's review.

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[263] ETH.MESH.00870466 at 467: Minutes - Ethicon Expert Meeting, Meshes for Pelvic Floor Repair, June 2, 2006.
[264] ETH.MESH.00081478: PROLIFT+M Pelvic Floor Repair System, Clinical Strategy, February 4, 2008.
[265] ETH.MESH.00372653 at 655: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[266] ETH.MESH.00748459 at 469: May 9, 2008, Response to FDA Letter on K071512: PROLIFT and PROLIFT+M Systems.
[267] ETH.MESH.02341454 at 455: Gynecare PROLIFT Instructions for Use (IFU) (in use 17 Dec 07 to 24 Sep 09 per IFU Index and Production Bates Range Chart).
[268] ETH.MESH.02341734 at 735: Gynecare PROLIFT Instructions for Use (IFU) (in use 1 Oct 09 to 7 May 10 per IFU Index and Production Bates Range Chart).
[269] ETH.MESH.00372653: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.

The final proposed labeling submitted to FDA prior to 510(k) clearance included an integrated summary of both studies (France and U.S.). This summary was not included in the IFU that was in use from December 17, 2007, through September 24, 2009,[270] and did not appear in the IFU until October 1, 2009.[271]

B. Patient Brochure (Patient Labeling)

Ethicon provided a Patient Brochure in response to FDA's request to do so,[272] advising FDA that "This brochure is used to aid in surgeon/patient communication and as an education tool for the patient. The brochure is distributed through marketing and is not part of the package labeling, as it is not intended to be used at the point of use of the device."[273] Notably, Ethicon had a Patient Brochure available for PROLIFT from at least November 9, 2005 (copy approval date).[274] Yet a Patient Brochure was not included in the "Proposed Labeling" section of the 510(k) (K071512) submissions prior to FDA's request for Ethicon to develop a Patient Brochure. Ethicon deviated from the standard of care for a medical device manufacturer by withholding the existing patient labeling until FDA requested it. The information that is required in a premarket notification submission includes "Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use."[275] The Patient Brochure that was submitted to FDA for review was the existing Brochure/copy approved November 15, 2006.[276] The revisions to the Brochure that were agreed with FDA prior to 510(k) clearance[277] are generally represented in the next version of the Brochure, for which copy was approved October 22, 2008, more than five months after 510(k) clearance. Importantly, however, the risk of injury to nerves of the pelvis was omitted from the October 2008 Brochure. The presentation of much of the information and the pictures also were changed.

Patient labeling is defined as any information associated with a device that is targeted to the patient (or lay caregiver).[278] The two general categories of information in patient labeling are risk/benefit information and instructions for use. For implants, such as the PROLIFT Mesh, patient labeling generally consists of risk/benefit information to help patients decide whether to have a device used on them and to allow patients to become aware of potential problems with the device. Patient labeling may also include descriptive

[270] ETH.MESH.02341454-459: Gynecare PROLIFT Instructions for Use (IFU) (in use 17 Dec 07 to 24 Sep 09 per IFU Index and Production Bates Range Chart).
[271] ETH.MESH.02341734-740: Gynecare PROLIFT Instructions for Use (IFU) (in use 1 Oct 09 to 7 May 10 per IFU Index and Production Bates Range Chart).
[272] ETH.MESH.00372653 at 656: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[273] ETH.MESH.00081328: Email with attachment, 18 Jan 2008, Bryan Lisa, Ethicon, to Jiyoung Dang, FDA RE: Teleconference K071512.
[274] ETH.MESH.03905968-975: Patient Brochure, copyright 2005, titled "Pelvic Organ Prolapse – Get the Facts, Be Informed, Make YOUR Best Decision," Approval Date: 11/9/2005 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[275] 21 CFR § 807.87(e).
[276] ETH.MESH.00748505 at 541: 2/21/08 Ethicon Response to December 20, 2007, FDA Letter RE: K071512 S04.
[277] ETH.MESH.00748459 at 491: May 9, 2008, Response to FDA Letter on K071512: PROLIFT and PROLIFT+M Systems.
[278] FDA Guidance on Medical Device Patient Labeling, April 19, 2001.

information about the device, types of patients for whom the device would not be a good choice, alternative therapeutic choices, and any other information to enable the person to make an informed decision about the device.[279]

Based on the Patient Brochures I reviewed and the letter from K.S. Crawford to Plaintiffs' Counsel documenting the final versions and approval dates of the Patient Brochures for the pelvic floor products,[280] there were four Patient Brochures specific for or relevant to PROLIFT, with the following Ethicon approval dates: 11/9/2005[281]; 11/15/2006[282]; 2/7/2007[283]; 10/22/2008.[284] (A fifth Patient Brochure, approval date 11/9/2009, was reviewed but is specific to PROSIMA and PROLIFT+M and so will not be discussed in this PROLIFT report.[285]) The first three of the Patient Brochures were in use (or approved by Ethicon for use) prior to 510(k) clearance of the PROLIFT System.

The "2005" and "2006" Brochures contained labeling issues such as the examples listed below:

- Reference to "Our **clinically proven** technologies" (There were no randomized, controlled clinical trials (RCTs) of PROLIFT to support this statement, no 510(k) clearance, and the TVM internal study report for the French trial, completed June 2006, showed the study did not meet the pre-defined criterion for effectiveness of a failure rate of less than 20% [upper limit of 90% CI].[286])
- Describes "**revolutionary** new minimally invasive surgical technique that offers **promising long-term results"** (There were no valid clinical data to support this statement from the 2005 Brochure. Note that FDA required Ethicon to remove the similar statement in the 2006 Brochure, plus the remainder of the Brochure page containing that statement, because the text presented on the page "is promotional, biased, and can be perceived as coercive to the patient to use your device."[287])

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[279] *Id.*
[280] May 21, 2012, Letter: In Re Pelvic Mesh/Gynecare Litigation – CT 291.
[281] ETH.MESH.03905968-975: Patient Brochure, copyright 2005, titled "Pelvic Organ Prolapse – Get the Facts, Be Informed, Make YOUR Best Decision," Approval Date: 11/9/2005 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[282] ETH.MESH.03905976-991: Patient Brochure, copyright 2006, titled "Pelvic Organ Prolapse – Get the Facts, Be Informed, Make YOUR Best Decision," Approval Date: 11/15/2006 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[283] ETH.MESH.03905992-6000: Patient Brochure, copyright 2007, titled "What's happening down there – let's talk about prolapse," Approval Date: 2/7/2007 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[284] ETH.MESH.03906037-052: Patient Brochure, copyright 2008, titled "Treatment Options for Pelvic Organ Prolapse – stop coping, start living," Approval Date: 10/22/2008 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[285] ETH.MESH.03906001-020: Patient Brochure, copyright 2011, titled "What you should know about Pelvic Organ Prolapse – stop coping, start living," Approval Date: 11/9/2009 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[286] ETH.MESH.00357123 at 126: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment[286] ETH.MESH.03906037-052: Patient Brochure, copyright 2008, titled "Treatment Options for Pelvic Organ Prolapse – stop coping, start living," Approval Date: 10/22/2008 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).
[286] ETH.MESH.03906001-020: Patient Brochure, copyright 2011, titled "What you should know about Pelvic Organ Prolapse – stop coping, start living," Approval Date: 11/9/2009 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel of genital prolapse.
[287] ETH.MESH.00372728 at 729: May 5, 2008, Email from J. Dang, FDA, to B. Lisa, Ethicon, RE:

- States "performed through very small incisions inside of the vagina" (There was no mention of the transgluteal approach and associated risks.)
- States "It allows for the **restoration of sexual function** by restoring normal vaginal anatomy." (There were no RCT data to support this statement, and conflicting data were reported in the TVM internal study reports, which were not completed until June 2006.)
- "GYNECARE PROLIFT will correct these defects and **restore normal support**." (There were no RCT data to support this statement, and the TVM internal study report for the French trial, completed June 2006, showed the study did not meet the pre-defined criterion for effectiveness of a failure rate of less than 20% [upper limit of 90% CI].[288])
- States "**appropriate for almost all patients**," complications **rare**, "**small risk** of the mesh material becoming exposed into the vaginal canal." (No valid clinical data existed to support these statements, and conflicting data concerning risks were reported in the TVM internal study reports and were also known to Ethicon through the medical literature and consultants. At the time Ethicon was making these statements, it knew that mesh exposure was a common complication and that the risk was not insignificant as communicated in the Patient Brochures. It was also aware that mesh contracture, although less common than mesh erosion, was a more serious complication that could cause vaginal anatomic distortion and lead to a negative impact on sexual function.[289] Ethicon's failure to communicate these risks constituted misbranding. Further, note that FDA required Ethicon to either provide supporting data from clinical studies or remove the statement that pelvic floor repair with PROLIFT is appropriate for most patients.[290] [See prior discussion regarding the latter statement in Section VI., 2.2.])
- Deceptive pictures (i.e., six pictures, all suggesting contentment, normal function [exercise, content husband/male partner], or physician confidence) (Emphasis added.)

The 2007 Patient Brochure is principally informational about prolapse and treatment options. While it subtly provides information on synthetic mesh for prolapse repair, it is not product specific. However, there is a lack of fair balance. For example, there is no discussion of risks (only instruction to ask your doctor about risks), yet there are statements that, "With the newer minimally invasive treatments, surgery time is reduced, recovery time is quicker, and many women can go home the next day." Additionally, the testimonial on the final page, accompanied by a picture of a contented woman, is misleading: "My life is so much simpler since my prolapse repair. I cannot count how many times I've said, 'This was so much easier than I had expected.'" Notably, by the time the copy for this Brochure was approved, there were

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Remaining deficiencies with K071512-Supplement 02 – Ethicon Prolift and Prolift+M.

[288] ETH.MESH.00357123 at 126: Clinical Study Report, Protocol Number CT-TVM-001-03, Evaluation of the TVM technique for treatment of genital prolapse.

[289] ETH.MESH.00081478-79: PROLIFT+M Pelvic Floor Repair System, Clinical Strategy, February 4, 2008.

[290] ETH.MESH.00372728 at 729: May 5, 2008, Email from J. Dang, FDA, to B. Lisa, Ethicon, RE: Remaining deficiencies with K071512-Supplement 02 – Ethicon Prolift and Prolift+M.

known complications with the PROLIFT, as discussed previously in this report, to the extent that the PROLIFT+M was in development as a "design improvement" of the PROLIFT "to minimize the mesh load given to the patient and increase the flexibility of the mesh that was being used in the pelvis," with the expectation that this would benefit the patient, both from a safety and effectiveness standpoint.[291]

The "2008" Patient Brochure contained labeling issues similar to those in the 2005 and 2006 Patient Brochures, as discussed above. Specific examples are shown below:

- States "performed through very small incisions inside of the vagina" (There was no mention of the transgluteal approach and associated risks.)
- States "simplifies the repairing process" (Ethicon knew in October 2004 from the "top 10 key learnings from the first TVM-Training course in Lille"[292] that the TVM procedure for PROLIFT placement is technically challenging, e.g., "The consensus is that some doctors will need more than one exposure to TVM surgery before they feel confident to be able to start the procedure (even those with high skill sets)." [293] Further, the Medical Director, Dr. David Robinson, acknowledged that preceptors for PROLIFT complained and brought to Ethicon's attention that less skilled trainees were too unskilled to do the PROLIFT and this was going to increase the complications for patients.[294])
- States patients "may experience less pain and quicker recovery," "patients can resume sexual intimacy" (According to Dr. Robinson, chronic pain and dyspareunia were known complications "from the start."[295] While "pain with intercourse" is noted later in the Brochure under "risks," on the page immediately following the discussion of "What are the risks," which is also the page that lists contraindications and risks (in small text), there is a sizeable picture (filling at least half of the page) of a laughing woman dancing with her male partner. Such a picture in this location is misleading and provides an overriding message of well-being.)
- Describes PROLIFT as "soft supportive mesh" (Yet by at least November 2006 Ethicon knew from a meeting with experts, including Professor Jacquetin, who created the product or was the leader of the team that created the product, that erosion and shrinkage were two primary issues with PROLIFT, and shrinkage, while less common, can be more severe. As a result, Ethicon was trying to find a way to address the PROLIFT problems of erosion and shrinkage.[296])
- Deceptive pictures (i.e., six pictures (including the one discussed above), all suggesting contentment, normal function [exercise, content husband/male partner], or physician confidence)

Importantly, risk information requested by FDA to be included in the Patient Brochure was missing until sometime after October 22, 2008, the copy approval date for the revised patient labeling, i.e., over five months after 510(k) clearance. Thus, patient

[291] David Robinson deposition transcript (rough draft), 3/14/12: 15:7-20, 24-16:13.
[292] ETH.MESH.02282833: Email series 07 Oct 2004, Subject: TVM – First training – key learnings.
[293] *Id.*
[294] Dr. David Robinson deposition, 3/14/2012, 377:10-378:2.
[295] Dr. David Robinson deposition, 3/13/2012, 311:2-312:12.
[296] Dr. David Robinson deposition, 3/14/2012, 447:24-449:1;450:19-451:24.

labeling was inadequate and fell below the applicable standard of care; specifically, it failed to inform patients about the potential for pain, scarring, pain during intercourse for both the patient and her partner, and that mesh exposure could result in the need for treatment, such as vaginal medication or removal of the exposed mesh. Ethicon's website contained similarly false and misleading information.[297] For example, as recently as January 2012, an Ethicon website continued to inform patients that the PROLIFT System was minimally invasive, that the risk of complications was rare, that there was only a small risk of erosion, and that it was appropriate for almost all patients including overweight patients, elderly patients, and patients that smoke.[298] As previously discussed, this information was false and misleading and known by Ethicon to be so for many years prior. For Ethicon not to update its website in a timely fashion falls below the standard of care for a reasonably prudent medical device manufacturer.

In summary, Ethicon's PROLIFT IFUs, Patient Brochures and its Website contained false and misleading information, as discussed above, and otherwise lacked fair balance.

OPINION #3: PROLIFT Misbranded - Failure to Warn and False or Misleading Labeling

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. For this reason, a device manufacturer must implement label changes in a timely manner as soon as possible after notice of any issues that may impact the safety or effectiveness of the device.[299] While labeling for prescription devices is premised on the concept that prescription devices are not safe for use except under the supervision of a licensed practitioner and, accordingly, are exempt from the "adequate directions for use" requirements applicable to OTC devices,[300] prescription device labeling nevertheless is required to contain information adequate for a licensed practitioner to use the device safely and effectively for its intended use.[301] Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[302]

In my professional opinion, based on my review of the PROLIFT labeling history and the IFU and patient labeling information discussed above, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of multiple labeling issues. Section 502 of the FDCA contains provisions on misbranding and the labeling issues that cause a product to be misbranded. The introduction or delivery for introduction into interstate commerce of any device that is misbranded is a violation of Section 301(a) of the FDCA.[303] Labeling issues that cause a device to be misbranded include labeling that is false or misleading in any particular[304]

[297] Plaintiff's Exhibit 241 to Scott Jones Deposition
[298] *Id*. at pgs 29, 33, 48 and 71
[299] Bryan Lisa deposition, 12/19/11, 293:12-294:18.
[300] 21 CFR § 801.109.
[301] 21 CFR § 801.109(c).
[302] 21 CFR § 801.109(d).
[303] 21 U.S.C. § 331(a).
[304] FDCA § 502(a), 21 U.S.C. § 352(a).

and labeling that does not bear adequate directions for use, including adequate warnings.[305]

The definition of "false or misleading" is not confined to meaning untrue, fraudulent, or deceptive. Labeling can be deemed by FDA to be misleading and in violation of FDA requirements if it proves deceptive to the customer by creating or leading to a false impression in the mind of the reader. Failure to inform the consumer of facts relevant to statements actually made may cause a "false impression," such that labeling that remains silent concerning certain consequences may be as deceptive as labeling that contains extravagant claims.[306] Labeling that fails to reveal material facts and consequences that may result from product use is considered misleading. A manufacturer's belief that physicians and/or patients may be aware of certain risks associated with its product is not a justification for failure to reveal material facts and consequences. Those risks must still be set forth fully and accurately in the product labeling.[307] Therefore, Ethicon's position that it was not necessary to warn physicians of risks it believed physicians already knew about the PROLIFT System is inconsistent with FDA requirements, and Ethicon's actions in not including those risks falls below the standard of care for a reasonably prudent medical device manufacturer.[308] The PROLIFT IFU, from market launch in early 2005 through at least October 1, 2009, is such an example of misleading labeling, as is the PROLIFT patient labeling, for the reasons discussed above.

Ethicon marketed the PROLIFT System without adequate instructions for use, and without adequate warnings about the potential risks, throughout the life of the product. As Ethicon's testimony has made clear, it knew of various risks associated with the PROLIFT that were not included in the IFU and patient labeling information.[309] Its delay of 16½ months in implementing the labeling agreed with FDA clearly falls below the standard of care of a reasonably prudent medical device manufacture.[310] Moreover, Ethicon represented to physicians from February 2005, prior to obtaining 510(k) clearance, that the PROLIFT was a line extension of GYNEMESH and covered by the GYNEMESH "approval,"[311] which, for the reasons presented elsewhere in this report, was false and misleading. Further, a substantially equivalent determination, or 510(k) clearance, of a device does not in any way constitute an official approval of the device. Accordingly, "[a]ny representation" (such as the reference to GYNEMESH "approval" in Ethicon's February 2005 letter to customers) "that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding."[312] The term "labeling" is interpreted by FDA broadly and may include any written materials that supplement or explain the product. The February

[305] FDCA § 502(f)(2).
[306] Medical Devices: Labeling Requirements – Misbranding (Available at fda.gov).
[307] Sean O'Bryan deposition, 5/18/12, 106:16-107:21.

[308] Piet Hinoul, 4/5/12: 326:21-330:23; 334:5-334:22; and 337:18-338:2.
[309] Piet Hinoul deposition, 4/5/12, 140:11-141:2; 298:14-299:21.
[310] Of note, Ethicon had previously opened a Corrective and Preventive Action Plan (CAPA) due to problems with timely implementing label changes in North America. ETH.MESH.00332860; See also Jennifer Paine Deposition 2/8/12, 70:14-73:9.
[311] ETH.MESH.00031323: February 8, 2005, Memo to Customer, copy to Regulatory File, Re: GYNECARE PROLIFT considered line extension of GYNECARE GYNEMESH.:
[312] 21 CFR § 807.97.

2005 customer letter constitutes labeling. In addition, Ethicon misrepresented to physicians, patients, and the American public in its response to the 2008 FDA *Public Health Notification* that Ethicon had obtained 510(k) clearance for the PROLIFT in 2005, when it knew such was not the case.[313]

VII. FDA ACTIONS: SERIOUS COMPLICATIONS ASSOCIATED WITH TRANSVAGINAL PLACEMENT OF SURGICAL MESH FOR PELVIC ORGAN PROLAPSE

A. 2008 *FDA PUBLIC HEALTH NOTIFICATION*

By 2008, FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) postmarket surveillance of the MAUDE database for medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature.

A search of the MAUDE database in 2008 showed that more than 1000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair POP and SUI.

As a result of these findings, FDA issued a *Public Health Notification* (PHN) in October 2008 informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients titled **"Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."**[314]

According to the 2008 PHN:

"The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia. Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses. Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

[313] Catherine Beath deposition, 3/27/12, 383:18-23

[314] FDA *Public Health Notification*: Serious Complications Associated with Transvaginal Placement of Surgical
Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, Issued October 20, 2008.

Recommendations Physicians should:

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."[315]

B. *2011 FDA SAFETY COMMUNICATION*

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for urogynecologic surgical mesh, with slightly more than half associated with POP repairs. On July 13, 2011, based on the 2008-2010 MAUDE database search and the FDA epidemiologic systematic literature review, the FDA issued a *Safety Communication* titled **"UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"**[316] to inform the medical community and patients that:

(1) serious complications associated with surgical mesh for vaginal repair of POP are **not rare** [Emphasis added.] (contrary to what was stated in the 2008 *PHN*), and

(2) it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

According to the *Safety Communication*:

"Although it is common for adverse event reporting to increase following an FDA safety communication, we are concerned that the number of adverse event reports remains high. From 2008 – 2010, the most frequent complications reported to the FDA for surgical mesh devices for POP repair include mesh erosion through the vagina (also called exposure, extrusion or protrusion), pain, infection, bleeding, pain during sexual intercourse (dyspareunia), organ perforation, and urinary problems. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage, and

[315] *Id.*

[316] FDA *Safety Communication*: UPDATE on Serious Complications Associated with Transvaginal Placement of
Surgical Mesh for Pelvic Organ Prolapse, Issued July 13, 2011.

emotional problems. Many of these complications require additional intervention, including medical or surgical treatment and hospitalization."[317]

Additionally:

"In order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date.

In particular, the literature review revealed that:

- Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
- Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results.

The FDA's literature review found that **erosion** of mesh through the vagina is the **most common and consistently reported mesh-related complication** from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication. **Mesh contraction** (shrinkage) is a **previously unidentified risk** of transvaginal POP repair with mesh that has been reported in the published scientific literature and in adverse event reports to the FDA since the Oct. 20, 2008 *FDA Public Health Notification*. Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain. Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion."[318] (Emphasis added.)

"The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh."[319]

The *Safety Communication* also provided a list of recommendations for health care providers and patients to consider for before and after transvaginal POP repair with mesh.[320]

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[317] *Id.*
[318] *Id.*
[319] *Id.*
[320] *Id.*

N.B.: In reference to FDA's above-noted statement that "[m]esh contraction (shrinkage) is a previously unidentified risk," it is important to note that this risk was known to Ethicon in November 2006, yet Ethicon did not disclose this information to FDA during the 510(k) (K071512) review, as discussed previously in this report. Specifically, Ethicon knew there were two issues with the PROLIFT from the perspective of some experts, including Professor Jacquetin, who created the PROLIFT product or was the leader of the team that created the product: erosions and shrinkage[321] In fact, the erosion and shrinkage problems were significant enough that Ethicon was trying to find a way to address them. [322] According to Dr. Robinson's testimony, both the mesh and the surgical technique can be factors leading to erosion.[323] As regards shrinkage, it was believed the responsibility of the mesh was more established. and "further to the expert's discussion, it was speculated that Ultrapro could be (not is) a solution for this problem, which is less common but can be more severe than erosion."[324]

Moreover, the known problem with shrinkage was a specific topic of discussion at the "Ethicon Expert Meeting: Meshes for Pelvic Floor Repair" on February 23, 2007.[325] The record notes that Professor M. Cosson remarked that "Polypropylene meshes might not be improvable in terms of shrinkage, we may need a completely new material."[326]

The fact that FDA did not learn about this risk until after the October 2008 *FDA Public Health Notification* emphasizes the importance of the manufacturer's responsibility for compliance with the Medical Device Reporting requirements (discussed further below). Additionally, FDA's public health and safety communications in both 2008 and 2011 support my previously-stated opinion that, had FDA been apprised of the adverse event issues about which Ethicon was aware prior to the submission of 510(k) number K071512, FDA would not have cleared the PROLIFT for marketing without adequate clinical evaluation, as FDA initially requested in its August 24, 2007, letter of 510(k) deficiencies.[327]

C. 2011 Meeting of Obstetrics and Gynecology Devices Advisory Committee and January 4, 2012, Update

Finally, in September, 2011, as a result of the above-discussed findings, FDA convened a meeting of the Obstetrics and Gynecology Devices Advisory Committee to discuss "Surgical Mesh For Treatment Of Women With Pelvic Organ Prolapse And Stress Urinary Incontinence." Based on the September 2011 Obstetrics-Gynecology Devices Panel meeting as well as assessment of Medical Device Reports (adverse event reports) submitted to the FDA and evaluation of the published literature, FDA announced in a

[321] Dr. David Robinson deposition, 3/14/2012. 447:10-448:15.
[322] Dr. David Robinson deposition, 3/14/2012, 451:17-24
[323] Dr. David Robinson deposition, 3/14/2012, 449: 20-24
[324] Dr. David Robinson deposition, 3/14/2012, 450:19-451:16.
[325] ETH.MESH.02017152: Ethicon Expert Meeting: Meshes for Pelvic Floor Repair, February 23, 2007, Minutes.
[326] ETH.MESH.02017152 at 153: Ethicon Expert Meeting: Meshes for Pelvic Floor Repair, February 23, 2007, Minutes.
[327]ETH.MESH.00372330 at 332: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.

January 4, 2012, Update, that it is "considering the recommendation that urogynecologic surgical mesh used for transvaginal repair of pelvic organ prolapse (POP) be reclassified from Class II to Class III."[328]

Further, FDA advised in the January 2012 Update that it continues to assess the safety and effectiveness of urogynecologic surgical mesh devices through a number of sources, including the published literature, epidemiological research on safety and effectiveness of surgical mesh, collaborations with professional societies and other stakeholders to fully understand the postmarket performance of urogynecologic surgical mesh devices and the occurrence of signs and symptoms associated with specific adverse events, and collecting and reviewing all available information about currently marketed urogynecologic surgical mesh devices.[329]

Additionally, on January 3, 2012, FDA issued 88 postmarket study orders to 33 manufacturers of urogynecologic surgical mesh for POP, including Ethicon. These orders mandate postmarket surveillance studies ("522 studies") and require the manufacturers to submit study plans to FDA to address specific safety and effectiveness concerns related to the surgical mesh devices for POP.[330]

D. Ethicon's Decision to Withdraw PROLIFT from the U.S. Market

Ethicon announced on June 5, 2012, that it would withdraw PROLIFT and three other of its mesh implants from the U.S. market. Ethicon "stressed that the move was not a recall, but was based on the products' commercial viability 'in light of changing market dynamics, and is not related to safety or efficacy.'"[331] The company stated it has requested approval from the FDA to stop "commercializing" the devices and that sales of the devices would be halted worldwide.[332]

VIII. POSTMARKET VIGILANCE ISSUES AND MISBRANDING

A. Significance of Postmarket Vigilance

"Postmarket vigilance" means all scientific and data collection activities related to the detection, evaluation, and understanding of adverse events. The primary objective of postmarket vigilance is to identify and evaluate any potential safety signal. The term "signal" refers to a potential safety issue or concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Importantly, in order for an event to be considered a signal, a causal relationship between the device and the event does not need to have been established. Postmarket vigilance is critical to ensuring that informed and timely decisions are made concerning medical device safety and, thereby, risk to patients is minimized.[333]

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[328] FDA UPDATE 01/04/2012: Urogynecologic Surgical Mesh Implants.
[329] *Id.*
[330] *Id.*
[331] Johnson & Johnson Unit to Halt Urinary Implants, by Katie Thomas, June 5, 2012, *The New York Times.*
[332] J&J Tells Judge It Will Stop Sales of Vaginal Implants, by Alex Nussbaum and Jef Feeley, June 5, 2012, *Bloomberg*.
[333] Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March 2005, U.S. FDA, CDER/CBER.

Safety signals can arise from multiple sources: postmarket data for a company's own product, including complaint reports from consumers made directly to the company, reports to FDA that are captured on the FDA's adverse event databases, and information from postmarketing clinical studies; scientific and medical literature; and events associated with other similar products. After a signal is identified, it should be further investigated to determine whether it represents a potential safety risk and whether other action should be taken. Such investigation may or may not lead to the conclusion that the device caused the event. FDA advises that a manufacturer should initially evaluate a signal through a careful review of individual case reports and a search for any additional cases. When one or more cases indicate a safety signal that needs further investigation, FDA recommends summarizing the available clinical information in order to characterize the potential safety risk and identify risk factors, if possible.

This section of my Report will discuss Ethicon's actions and inactions according to the MDR regulations and other postmarket vigilance activities. Information that was known or knowable to Ethicon will be addressed according to the various sources from which safety signals can arise, as listed above.

B. Scientific and Medical Literature: Reported Mesh Complications

There are few prospective clinical trials comparing no-mesh versus mesh-supported surgery for pelvic organ prolapse. Of those studies reviewed and discussed in this report, the authors were in agreement (as previously discussed) that additional studies still are needed to assess the risk/benefit of the use of mesh, particularly nonabsorbable mesh such as PROLIFT, for the correction of POP. While most studies agree that the use of mesh increases the cure rate based on anatomic outcome, there is little difference between no-mesh and mesh-supported surgery in subjective cure of symptoms when these have been reported, and use of mesh is associated with more complications. As a result, authors of the studies reviewed question the value of using synthetic mesh for POP repair and voice concerns about the risk vs. benefit. Prior to the initial marketing of PROLIFT in early 2005 and the PROLIFT+M 510(k) submission in 2007 (expanded to include PROLIFT), the literature relevant to the use of mesh for POP repair was limited, but published articles provided evidence that the potential for complications associated with use of mesh was known in 2005-2007. Relevant articles are individually summarized in Appendix C.

For example, in one prospective, observational study of 63 women who underwent surgery for vaginal prolapse using PROLENE (polypropylene) mesh, dyspareunia increased by 20% in those patients who had anterior repair (32) and by 63% in those who had posterior repair (31). Mesh erosion occurred in 13% and 6.5% of those who underwent anterior and posterior repair, respectively. While the study showed good anatomical results, the authors concluded that the use of PROLENE mesh should be abandoned due to the high rate of morbidity.[334] In a retrospective study of 277 women who underwent surgery for POP repair using a transvaginal mesh technique with

[334] Milani R et al. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. *BJOG* 2005;112:107-111.

polypropylene mesh, 34 cases (12%) of mesh exposure were observed, 25 of which required partial mesh excision. The authors concluded that caution was warranted when using this new technique and that clinical trials and experimental studies were needed to reduce mesh exposures.[335] A case report of a 47-year-old woman who underwent a laparoscopic supracervical hysterectomy and a posterior repair with polypropylene mesh reported rectal erosion requiring excision and subsequent persistent dyspareunia and pain requiring complete vaginal removal of the mesh. These authors also concluded that further studies were needed to determine the safety and efficacy of transvaginally placed synthetic mesh.[336]

Dr. David Robinson, Medical Director at Ethicon, provided deposition testimony that chronic pain and dyspareunia were known to be potential complications "from the start."[337] He testified these complications weren't confirmed in Ethicon's own studies, but that "What we were seeing was appearance in the literature."[338] Notably, a review of Ethicon's two TVM internal study reports (discussed previously in this report) shows that the number of patients in the French study who were not having sexual activity for a reason other than prolapse was much higher at 12 months after surgery, with 12.6% of patients exhibiting moderate or severe vaginal retraction. Additionally, the mesh exposure rate was 10% in this study, and more than 25% of patients (25.6%) experienced one or more serious adverse events. In the U.S. study, the mesh exposure rate was 14.1%, while 20% of patients experienced urinary incontinence, and 10.6% experienced void dysfunction. Based on my knowledge, training, and experience in the conduct of clinical trials, these complication rates are significant. Additionally, the mesh exposure rates are consistent with those rates discussed above that led the study authors to conclude further studies were needed to reduce mesh exposures. Yet, in response to FDA's request of Ethicon, during the 510(k) (K071512) review, to provide a clinical evaluation for the PROLIFT, Ethicon replied as shown below, along with FDA's request and rationale:

> *"..This complex procedure is proposed to be done in a 'blind' manner through the use of the specialized surgical tools provided in the Gynecare System. Due to the complexity of this procedure and potential high risk for organ perforation, bench testing is not sufficient to demonstrate device safety and efficacy. Please provide a clinical evaluation of your proposed Prolift System to support your Indications for Use."*
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> "...Ethicon believes that the results of pre-clinical, benchtop testing, and cadaver evaluations, provide evidence of substantial equivalence of the PROLIFT Systems to the currently marketed GYNEMESH and demonstrate that surgeons can use the device without problems."[339]

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[335] Collinet P et al. Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. *Int Urogynecol J* 2006;17:315-320.
[336] Hurtado EA et al. Rectal erosion of synthetic mesh used in posterior colporrhaphy requiring surgical removal. *Int Urogynecol J* 2007;18:1499-1501.
[337] Dr. David Robinson deposition, 3/13/2012, 311:2-312:12.
[338] Dr. David Robinson deposition, 3/13/2012, 311:8-17.
[339] ETH.MESH.00372341 at 345-347: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.

C. Medical Device Reporting/MAUDE and Issue Reports

As discussed previously in this report, medical device manufacturers are required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions, in accordance with the Medical Device Reporting (MDR) regulations.[340] Medical Device Reporting provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order to detect and correct safety problems in a timely manner. Achieving the purpose of Medical Device Reporting is dependent on the compliance and cooperation of the medical device manufacturer. MDR reports submitted to FDA are entered into the Manufacturer and User Facility Device Experience (MAUDE) Database, which contains reports of adverse events involving medical devices. The MAUDE database includes not only MDRs from manufacturers but also MDR reports from user facilities and voluntary reports from such sources as healthcare practitioners, patients, and consumers. The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[341]

To evaluate the serious adverse event information known or knowable to Ethicon based on the MAUDE database, an independent search/review of the MAUDE database for Ethicon vaginal mesh-reported adverse events was undertaken. Summary results of that review are presented below. The methodology used is described in detail in Appendix E, and the tabulations supporting the summary results also are provided in Appendix E.

1. Summary of MAUDE Adverse Event Reports

A total of 968 MAUDE Adverse Event Reports for all Ethicon mesh products (excluding intra- and perioperative events) were located by the search methods described in Appendix E. This search yielded 167 reports for GYNEMESH, 552 reports for PROLIFT, and 112 reports for PROLIFT+M. It also includes 137 reports for other Ethicon mesh products. The most often reported adverse events were mesh erosion or exposure, pain and dyspareunia. These events were reported in 74.3% (719), 47.4% (459) and 19.8% (192) of the reports, respectively. Of these MDRs, 68.2% (660) reported the need for follow-up surgery as a result of the reported events. The number of reports by year for these events is represented in Table 2.1 below.

In addition, the search for selected other mesh products that have been used for gynecological indications yielded 130 reports for Apogee, Perigee and other "unknown" mesh products. Mesh erosion or exposure, pain and dyspareunia were reported in 59.2% (77), 43.1% (56) and 34.6% (45) of the reports, respectively. Of these MDRs, 52.3% (68) reported the need for follow-up surgery as a result of the reported events. The number of reports by year for these events is represented in Table 2.2 below.
Other frequently reported adverse events include urinary tract infections (UTIs), urinary

[340] 21 CFR Part 803.
[341] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

incontinence, scar tissue and/or granuloma, vaginal discharge and/or odor, and neurological compromise to structures and tissues. In addition, reports of cystocele, rectocele, fistula, and deformed mesh were also prevalent.

There was at least one follow-up report for 11.4% (114) of the 997 MDRs (including intra- and perioperative events) for all Ethicon products searched. While the FDA received most initial reports within 31 days of manufacturer receipt of the report, there were a number of reports with a somewhat longer reporting interval. Of note, however, are eight reports with reporting intervals that were between 116 and 262 days.

The frequency of all events, treatments, follow-up reports and intervals between manufacturer and FDA receipt of the reports are tabulated in Appendix E, Section II. A detailed analysis of each report can be found in Appendix E, Section III.

Table 2.1: All Ethicon Mesh Products Combined - Most Commonly Reported Events

Year	Reports	Mesh Erosion or Exposure	Pain	Dyspareunia
	n	n	n	n
2002	1	1	1	
2004	10	4	2	1
2005	52	22	3	3
2006	48	27	10	4
2007	61	31	18	17
2008	75	51	18	14
2009	129	80	39	39
2010	161	125	81	38
2011	282	239	168	63
2012^	149	139	119	13
Total	**968**	**719 (74.3%)**	**459 (47.4%)**	**192 (19.8%)**

^ Jan – 31 March 2012

Table 2.2: Apogee, Perigee and "Unknown Manufacturer Mesh Product" Combined - Most Commonly Reported Events

Year	Reports	Mesh Erosion or Exposure	Pain	Dyspareunia
	n	**n**	**n**	**n**
2006	8	3	7	
2007	17	7	5	6
2008	32	23	11	12
2009	36	23	16	10
2010	2	1	1	1
2011	34	19	15	15
2012^	1	1	1	1
Total	**130**	**77 (59.2%)**	**56 (43.1%)**	**45 (34.6%)**

^ Jan – 31 March 2012

1.1. GYNEMESH MAUDE Adverse Event Reports

A total of 141 Manufacturer MDRs and 26 voluntary MedWatch reports, for the years 2004 - March 2012 were located from this search. Of note, two of the manufacturer MDRs were for more than one person.

These 167 total reports include 379 separate symptoms/events. A majority of these reports, specifically, 67.1% (112 of 167) included a report of mesh erosion or exposure; 34.7% (58 of 167) included a report of pain, and 20.4% (34 of 167) included a report of dyspareunia. In addition, 15.6% (26 of 167) of the MDRs included at least one urinary tract infection (UTI). The number of reports by year for these events is presented in Table 2.3 below.

Table 2.3: GYNEMESH Most Commonly Reported Events

Year	Reports	At least one follow-up report	Mesh erosion or exposure	Pain	Dyspar-eunia	UTI
	n	n	n	n	n	n
2004	10	1	4	2	1	0
2005	47	10	20	2	3	22
2006	15	0	11	4	1	0
2007	22**	0	14	6	8*	1
2008	3	0	3	1	1	0
2009	16	0	15	6	7	0
2010	19	0	15	14	2	0
2011	29	14	25	20	10	2
2012^	6	4	5	3	1	1
Total	167**	29	112 (67.1%)	58 (34.7%)	34* (20.4%)	26 (15.6%)

^Jan-31 Mar 2012
* One report represents more than one person.
** Two reports represent more than one person, 4 reports do not include information regarding the type of adverse event.

The following events which were included in fewer than 8.5% of the MDRs accounted for an additional 149 separate symptoms/events: urinary incontinence (stress, urge or unspecified) (9 reports); rectocele or cystocele (12 reports); prolapse (6 reports); fistula (9 reports); scar tissue and/or granuloma (10 reports); neurological compromise to structures and tissues (5 reports); vaginal discharge and/or odor (14 reports); and deformed mesh (4 reports). Other less frequently reported adverse events were grouped together for purposes of this Report and are categorized under "other"; such events may include, but are not limited to, any of the following: surgical complications, bleeding, hematoma, fever, infection, abscess, inflammation, urinary retention, urinary urgency, bladder stone, problems with bowel movements, constipation, and trouble standing and/or walking. They may also be unspecified or represent more than one symptom.

At least one treatment was reported in 93.4% (156 of 167) of the reports. This included surgery or planned surgery for 59.3% (99 of 167) of the reports, trimming of the mesh for 11.4% (19 of 167) of the reports and other treatments, including, but not limited to antibiotics, hormone and/or antibiotic cream and pain medication for 34.7% (58 of 167) of the reports.

Of note, throughout this analysis, not every single "other" treatment was counted; instead "classes" of products and treatments were counted. For example, any number of antibiotics or surgeries described for a particular report was counted only once.

In addition to the above events, there were 27 reports of post-surgical (perioperative) complications for the years 2004 through 2010. Four reports were stated to be surgical complications, 10 were perioperative complications, and the temporal relation to surgery could

not be determined for five reports. There were also eight surgical or perioperative reports that were specifically stated to involve the device, or based on the narrative and comments in the report, were suggestive of device involvement. One of these patients experienced bowel perforation and an infected hematoma. In the opinion of the surgeon, this patient died from multiple organ failure from sepsis due to bowel perforation related to the surgery. This report was made in 2008, and the patient also had an unspecified sling. The 27 MDRs included three (11.1%) reports each of pain, mesh erosion/exposure and fistula, and two (7.4%) reports of vaginal discharge and/or odor.

Of the 168 total manufacturer reports for GYNEMESH, 16.7% (28 of 168) of the reports had at least one follow-up report. Also, the FDA received 8.3% (14) of the 168 manufacturer reports greater than 31 days after manufacturer receipt of the report, with the reporting interval being 116, 119, 173 and 262 days for four 2005 reports. The reporting intervals for the remainder of the reports were all between 32 and 36 days (7 reports) and 42 and 47 days (3 reports).

1.2. PROLIFT MAUDE Adverse Event Reports

A total of 513 Manufacturer, 4 User Facility, and 35 voluntary MedWatch Reports, for the years 2005 - March 2012 were located from this search. Of note, five of the Manufacturer MDRs represent adverse events for more than one person. These 552 reports include 1,479 separate symptoms/events, including two deaths. One report in 2010 reported that "the mesh eroded into the patient's bladder, caused an infection, and led to her death." The cause of death was listed as bladder mesh, sepsis, and anemia." In addition, in 2011, one patient with "many unspecified problems" and severe pain and constipation who also had a Uretex synthetic sling committed suicide. Of these reports, 77.9% (430 of 552) included a report of mesh erosion or exposure, 49.1% (271 of 552) included a report of pain, and 21.4% (118 of 552) included a report of dyspareunia. Scar tissue and/or granuloma were reported in 16.5% (91 of 552) of the reports, and neurological compromise to structures and tissues was reported in 14.3% (79 of 552) of the reports. The number of reports by year for these events is presented in Table 2.4 below.

Table 2.4: PROLIFT Most Commonly Reported Events

Year	Reports	At least one follow-up report	Mesh erosion or exposure	Pain	Dyspa-reunia	Scar tissue/ granulo ma	Neuro compro-mise
	n	n	n	n	n	n	n
2005	3	0	2	0	0	0	0
2006	31	0	15	5	3	0	0
2007	37^^	1	16	12	9	1	0
2008	55	1	39	13	12	1	1
2009	71***	1	46**	27*	30*	22	17
2010	107	0	89	51	25	13	12
2011	164	50	144	96	33	40	37
2012^	84	7	79	67	6	14	12
Total	552***	60	430** (77.9%)	271* (49.1%)	118* (21.4%)	91 (16.5%)	79 (14.3%)

^Jan-31 Mar 2012
* One report represents more than one person.
** Two reports represent more than one person.
*** Five reports represent more than one person.
^^Two reports do not include information regarding the type of adverse event.

The following events which were included in fewer than 8% of the MDRs accounted for an additional 490 separate symptoms/events: at least one UTI (22 reports); vaginal discharge/odor (34 reports); urinary incontinence (stress, urge or unspecified) (43 reports); rectocele or cystocele (16 reports); prolapse (27 reports); fistula (18 reports); and deformed mesh (28 reports). Other less frequently reported adverse events were grouped together for purposes of this Report and are categorized under "other"; such events may include, but are not limited to, any of the following: surgical complications, bleeding, hematoma, fever, infection, abscess, inflammation, urinary retention, urinary urgency, bladder stone, problems with bowel movements, constipation, and trouble standing and/or walking. They may also be unspecified or represent more than one symptom.

At least one treatment was reported in 82.4% (455 of 552) of the reports. This included surgery or planned surgery for 72.3% (399 of 552) of the reports, trimming of the mesh for 6.2% (34 of 552) of the reports and other treatments, including, but not limited to, antibiotics, hormone and/or antibiotic cream, and pain medication for 18.1% (100 of 552) of the reports.

In addition to the above events, there were 64 reports of perioperative complications for the years 2005 through 2011. Thirteen reports were stated to be surgical complications, 18 were perioperative complications and there were 33 surgical or post-surgical reports that were specifically stated to involve the device, or based on the narrative and comments in the report, were suggestive of device involvement. The 64 MDRs included six (9.4%) reports of mesh erosion/exposure, four (6.3%) reports of fistula and three (4.7%) reports of pain.

Of the 577 total manufacturer reports for PROLIFT, 10.9% (63 of 577) of the reports had at least one follow-up report. Also, the FDA received 4.0% (23) of the 577 manufacturer reports greater than 31 days after manufacturer receipt of the report, with the reporting interval being between 45 and 74 days for four reports and between 32 and 35 days for the remainder (21) of the reports.

1.3. Prolift+M MAUDE Adverse Event Reports

A total of 111 manufacturer MDRs and one voluntary MedWatch report, for the years 2008 - March 2012 were located from this search. These 112 reports include 207 separate symptoms/events, including one death. Of these MDRs, 59.8% (67 of 112) included a report of mesh erosion or exposure, and 27.7% (31 or 112) included a report of pain. In addition, 11.6% (13 of 112), 10.7% (12 of 112), 9.8 % (11 of 112) ,and 9.8% (11 of 112) of the reports included scar tissue and/or granuloma, dyspareunia, neurological compromise to structures and tissues, and urinary incontinence (stress, urge or unspecified), respectively. The number of reports by year for these events is presented in Table 2.5 below.

The reported death involved a sigmoid perforation by the right posterior arm of the mesh and enterococcemia in a patient who underwent a laparotomy after presenting with paralytic ileus, urinary stasis and a hematoma on the first post-operative day. The patient was treated with antibiotics, went home and returned for emergency hospitalization with signs of septic shock. The patient was placed on artificial respiration, underwent another laparotomy and expired due to multi-organ failure with urosepsis. The manufacturer's narrative for this report concluded that the device instructions provide warnings to use the device "with care and with attention to patient anatomy and to proper dissection technique, to avoid damage to vessels, nerves, bladder, bowel and vaginal wall perforation. Users should be familiar with surgical procedures and techniques involving pelvic floor repair and synthetic meshes before employing the Gynecare Prolift+M systems." This report was made in 2010.

Table 2.5: Prolift+M Most Commonly Reported Events

Year	Reports	At least one follow-up report	Mesh erosion or exposure	Pain	Dyspar-eunia	Scar tissue/ granu loma	Neuro compromise	Incon-tinence
	N	n	n	n	n	n	n	n
2008	13	0	6	2	0	0	0	1
2009	39	2	17	3	1	1	0	7
2010	14	0	5	3	2	0	0	0
2011	25	12	19	7	7	10	9	1
2012^	21	2	20	16	2	2	2	2
Total	112	16	67 (59.8%)	31 (27.7%)	12 (10.7%)	13 (11.6%)	11 (9.8%)	11 (9.8%)

^Jan-31 Mar 2012

The following events which were included in fewer than 8% of the MDRs accounted for an additional 62 separate symptoms/events: rectocele or cystocele (5 reports); prolapse (6 reports); vaginal discharge and/or odor (3 reports); at least one UTI (8 reports); and deformed mesh (4 reports). Other less frequently reported adverse events were grouped together for purposes of this Report and are categorized under "other"; such events may include, but are not limited to, any of the following: surgical complications, bleeding, hematoma, fever, infection, abscess, inflammation, urinary retention, urinary urgency, bladder stone, problems with bowel movements, constipation, and trouble standing and/or walking. They may also be unspecified or represent more than one symptom.

At least one treatment was reported in 84.0% (94 of 112) of the reports. This included surgery or planned surgery for 59.1% (55 of 112) of the reports, trimming of the mesh for 16.1% (18 of 112) of the reports, and other treatments, including, but not limited to antibiotics, hormone and/or antibiotic cream, and pain medication for 42.9% (48 of 112) of the reports.

In addition to the above events, there were 12 reports of perioperative complications for the years 2008 through 2011. Four reports were stated to be post-surgical complications and both intra- and post-operative complications were described in one 2010 report. This patient expired from a pulmonary embolism following repeat surgery to remove a sponge that had been retained in her pelvic cavity during the initial surgery for a Solyx sling and a pelvic floor repair procedure. There were also seven surgical or post-surgical reports that were specifically stated to involve the device, or based on the narrative and comments in the report, were suggestive of device involvement.

Of the 123 total manufacturer reports for PROLIFT+M, 13.0% (16 of 123) of the reports had at least one follow-up report. Also, the FDA received 13.0% (16) of the 123 manufacturer reports greater than 31 days after manufacturer receipt of the report, with the reporting intervals being 73 days, 144 days, 176 days and 183 days for four 2009 reports, 167 days for one 2011 report, and between 32 and 34 days for the remainder (11) of the reports.

1.4. Other Ethicon Mesh Products

A total of 127 Manufacturer and 10 voluntary MedWatch Reports, for the years 2002 - March 2012 were located from this search, which includes 34 reports for PROLENE, one report for PROLENE Soft and 101 reports for an unspecified Ethicon mesh. Of note, for three of the unspecified mesh reports, it could not be confirmed if the report was for a gynecological indication. These 137 reports included 403 separate symptoms/events. Of these reports, 80.3% (110 of 137) included a report of mesh erosion or exposure, 72.3% (99 of 137) included a report of pain, 38% (52 of 137) included a report of neurological compromise of structures and tissues, and 20.4% (28 of 137) included a report of dyspareunia. Urinary incontinence (stress, urge or unspecified) was reported in 9.5% (13 of 137), and scar tissue and/or granuloma was reported in 8.0% (11 of 137) of the reports. The number of reports by year for these events is presented in Table 2.6 below.

Table 2.6: Other Ethicon Mesh Products Most Commonly Reported Events

Year	Re-ports	At least one f/u* report	Mesh ero or expo**	Pain	Dyspar-eunia	Scar tissue/ granuloma	Neuro compro-mise	Incon-tinence
	N	n	n	n	n	n	n	n
2002	1		1	1				1
2005	2	1		1				
2006	2		1	1				
2007	2		1					
2008	4		3	2	1			2
2009	3		2	3	1			1
2010	21		16	13	9	1	4	1
2011	64^^	5	51	45	13	9	26	8
2012^	38	4	35	33	4	1	22	
Total	137	10	110 (80.3%)	99 (72.3%)	28 (20.4%)	11 (8.0%)	52 (38 %)	13 (9.5%)

^Jan-31 Mar 2012
* At least one follow-up report
** Mesh erosion or exposure
^^ For one report, unspecified mesh was used and for another report, the patient had a pelvic floor repair, in addition to TVT which was the main product for that surgery.

The following events, which were included in fewer than 4% of the reports, accounted for an additional 81 separate symptoms/events: vaginal discharge/odor (3 reports); rectocele or cystocele (1 report); prolapse (5 reports); and fistula (3 reports). At 11.7% (16 of 137), the rate of deformed mesh was somewhat higher for this group compared to the afore-mentioned products. Other less frequently reported adverse events were grouped together for purposes of this Report and are categorized under "other"; such events may include, but are not limited to, any of the following: surgical complications, bleeding, hematoma, fever, infection, abscess, inflammation, urinary retention, urinary urgency, bladder stone, problems with bowel movements, constipation, and trouble standing and/or walking. They may also be unspecified or represent more than one symptom.

At least one treatment was reported in 82.5% (113 of 137) of the reports. This included surgery or planned surgery for 78.1% (107 of 137) of the reports, trimming of the mesh for 6.6% (9 of 137) of the reports, and other treatments, including, but not limited to, antibiotics, hormone and/or antibiotic cream, and pain medication for 6.6% (9 of 137) of the reports.

In addition to the above events, for PROLENE, there were two reports of surgical or postsurgical reports that were specifically stated to involve the device, or based on the narrative and comments in the report, were suggestive of device involvement. These two MDRs included one report of mesh erosion/exposure and one report of fistula.

Of the 129 total manufacturer reports for PROLENE, PROLENE SOFT and unspecified Ethicon mesh products combined, 7.8% (10 of 129) of the reports had at least one follow-up report. Also, the FDA received one manufacturer report 33 days after manufacturer receipt of the report.

1.5. Other Manufacturer Mesh Products, including Apogee, Perigee and "Unknown Manufacturer"

A total of 56 Manufacturer and 74 voluntary MedWatch Reports, for the years 2006 - March 2012 were located from this search, which includes 9 and 18 reports for Apogee and Perigee, respectively. These 130 reports included 302 separate symptoms/events. Of these reports, 59.2% (77 of 130) included a report of mesh erosion or exposure, 43.1% (56 of 130) included a report of pain, and 34.6% (45 of 130) included a report of dyspareunia. Urinary incontinence (stress, urge or unspecified) was reported in 17.7% (23 of 130), and vaginal discharge and/or odor was reported in 11.5% (15 of 130) of these reports. The number of reports by year for these events is represented in Table 2.7 below.

Table 2.7: Other Manufacturer Mesh Products Most Commonly Reported Events

Year	Reports	Mesh erosion or exposure	Pain	Dyspar-eunia	Incon-tinence	Discharge/ Odor
	n	n	N	n	n	n
2006	8	3	7			
2007	17	7	5	6	2	
2008	32	23	11	12	5	6
2009	36	23	16	10	7	4
2010	2	1	1	1		1
2011	34	19	15	15	9	4
2012^	1	1	1	1		
Total	130	77 (59.2%)	56 (43.1%)	45 (34.6%)	23 (17.7%)	15 (11.5%)

^Jan-31 Mar 2012

The following events, which were included in fewer than 5% of the reports accounted for an additional 77 separate symptoms/events: rectocele or cystocele (3 report); prolapse (6 reports); fistula (2 reports); scar tissue and/or granuloma (6 reports); and deformed mesh (4 reports). Other less frequently reported adverse events were grouped together for purposes of this Report and are categorized under "other"; such events may include, but are not limited to, any of the following: surgical complications, bleeding, hematoma, fever, infection, abscess, inflammation, urinary retention, urinary urgency, bladder stone, problems with bowel movements, constipation, and trouble standing and/or walking. They may also be unspecified or represent more than one symptom.

At least one treatment was reported in 69.2% (90 of 130) of the reports. This included surgery or planned surgery for 52.3% (68 of 130) of the reports, trimming of the mesh for 18.5% (24 of 130) of the reports, and other treatments, including, but not limited to, antibiotics, hormone and/or antibiotic cream, and pain medication for 28.5% (37 of 130) of the reports.

In addition to the above events, there were nine reports of perioperative complications for the years 2005 through 2009. Three reports were stated to be perioperative complications, and the temporal relation to surgery could not be determined for one report. There were also five surgical or perioperative reports that were specifically stated to involve the device, or based on the narrative and comments in the report, were suggestive of device involvement. These nine reports included one fistula.

1.6. Other Indications for Implantable Mesh Products

It is important to note that this search, conducted as described in Appendix E, also yielded 26 reports for PROLENE from which it could not be clearly determined that the device had been used in a gynecological procedure. Since PROLENE is indicated for "use in hernia repair or other fascial defects," these 26 reports have not been included in this analysis.

Also of importance is that, while conducting the "Ethicon mesh" simple search, it was noted that there are MDRs for other Ethicon mesh products. In particular, there are a very large number of reports for Tension Free (TVT) Vaginal Tape. There are also many reports for PROCEED and ULTRAPRO MESH. These have not been included in the analysis for this report.

2. Ethicon Issue Reports

Of 242 PROLIFT Issue Reports reviewed (date range: January 1, 2005, through December 31, 2009), 126 were submitted as MedWatch (MDR) reports to FDA, and 116 were determined to be "not reportable." Review of the "not reportable" events showed a number of these were due to device "malfunction" which the surgeon dealt with during surgery. "Malfunction" is defined as a "failure of a device to meet its performance specifications or to perform as intended."[342] Three examples are given below:

- "[W]hile pulling posterior arms/straps through cannula on patient's left side, mesh arm broke off. Remnants of mesh reinforced with suture to deliver mesh into cannula for tensioning. Case completed satisfactorily. No adverse patient outcome."[343]

  The rationale for not reporting this event was that "the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure."[344] Note, however, that the Instructions for Use state as a Precaution to "Avoid placing excessive tension on the mesh implant during placement."[345]

[342] 21 CFR § 803.3.
[343] ETH.MESH.02646697: Tracking # 10100063476 - Issue Report, December 5, 2007, Alert Date.
[344] ETH.MESH.02646697 at 699: *Id.*
[345] ETH.MESH.02341658 at 659: Gynecare PROLIFT Instructions for Use (IFU), STATUS: 02/2010 (in use 11 May 2010 to present day per IFU Index and Production Bates Range Chart).

- Device was used for an anterior repair with a "cysto" and "TVT." "[M]esh broke while the surgeon was attempting to pull the mesh through the skin trocar. The surgeon removed the portion of the mesh that had broken and used the remaining piece (approx. 1 inch) by attaching it to the posterior part of the anterior vagina. There were no patient consequences. The procedure was extended by about 10-15 minutes." "[B}ladder was punctured during trocar insertion," and "surgeons chose to allow the bladder to heal without medical treatment." It was also noted that the bladder "puncture added about 20 minutes to the procedure."[346]

  The rationale for not reporting this event was that "the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with this device, with another device or treatment modality, or completely abort the procedure."[347]

- Arm on PROLIFT ripped in half when pulling through cannula. Original mesh was pulled out, new one was opened and the procedure was completed without patient consequence.[348] (Note that NCR07-11350 was assigned to address the issue with the mesh.)[349]

  The rationale for not reporting this event was that "the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure."[350]

  The summary for this Issue Report noted that, "In the last 12 month [sic] we received 5 complaint [sic] on Prolift for fraying or tears on the mesh, all on different or unknown lot numbers."[351]

Medical Device Reporting requires that a manufacturer report a malfunction to FDA if the device or a similar device it markets would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.[352] The regulation assumes that a malfunction will recur.[353] FDA has determined that a malfunction is reportable if it meets any one of several criteria, two of which are applicable to the PROLIFT, as follows:

[346] ETH.MESH.02646702: Tracking # 10100064356 - Issue Report, January 21, 2008, Alert Date.
[347] ETH.MESH.02646702 at 704: *Id.*
[348] 345 ETH.MESH.02646594: Tracking #10100058857 – Issue Report, October 16, 2007, Alert Date
[349] ETH.MESH.02646594 at 595: *Id.*
[350] ETH.MESH.02646594 at 597: *Id.*
[351] ETH.MESH.02646594 at 598: *Id.*
[352] 21 CFR § 803.50(a).
[353] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.

- "it causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring, or diagnostic effectiveness which could cause or contribute to a death or serious injury;
- the device involves a long-term implant..."[354]

Notably, "[M]alfunctions of long-term implants are not routinely or 'automatically' reportable unless the malfunction is likely to cause or contribute to a death or serious injury if it recurs."[355] "Serious injury" includes injury that "results in permanent impairment of a body function or permanent damage to a body structure," or injury that "[n]ecessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. "Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage."[356] Of note, Dr. David Robinson, Medical Director, was unable to provide the regulatory definition of "serious," as illustrated by his deposition testimony below:

> Q. If a woman were to be unable to void her bladder in a normal fashion without self-catheterizing for a year, would that be a serious complication?
> A. Well, I think – I don't know if – there's a definition that's used for serious within trial language. Outside of that definition, then it becomes an individual's interpretation of what is serious or not serious.[357]

Ethicon documented in the Device Design Safety Assessment (DDSA) for the PROLIFT, on the "Use Related Hazard Worksheet," that if a user uses the device in a manner other than that described in the Instructions for Use, "[R]amifications could range from device failure to patient harm,[358] as identified in the DDSA Form. The applicable "Hazard" specified on the DDSA Form is "Inadequacy of performance characteristics for the intended use,"[359] for which the "Severity of Harm" ranking is "4," defined as "Severe," for example:

- "The therapy/procedure is abandoned/delayed due to failure of the product. Product replacement is required to complete the therapy/procedure and it is reasonable to assume that replacements are not readily accessible.
- Failure causes reversible patient health and safety concerns, and addressing failure causes the procedural time to be significantly increased." (Significant increase in procedural time is defined as an increase more than 30 minutes for procedures where the patient is under general anesthesia and more than 60 minutes for procedures where the patient is under local or no anesthesia.)
- "Addressing the device failure...requires administration of pharmaceuticals and/or surgical intervention not normally required for standard post-operative therapy which may delay patient recovery and/or complicate the planned medical therapy."[360]

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[354] *Id*
[355] FDA Compliance Program Guidance Manual 7382.845, Attachment C.
[356] 21 CFR § 803.3.
[357] Dr. David Robinson deposition, 3/13/2012, 70:12-20.
[358] ETH-03533 at 550: PROLIFT Product Device Design Safety Assessment, Revision C, 2/25/2005, Appendix IV.
[359] ETH-03533 at 560: PROLIFT Product Device Design Safety Assessment, Revision C, 2/25/2005, Appendix VI.
[360] ETH-03533 at 560: PROLIFT Product Device Design Safety Assessment, Revision C, 2/25/2005, Appendix VII.

Notably, the applicable "Probability of Hazard" was ranked "2,"[361] defined as "rare," i.e., "<1 failure in 1 year."[362]

The Issue Reports reviewed document that the "Probability of Hazard" ranking in the DDSA was wrong. In fact, the ranking was "5" or "Frequent," i.e., <1 failure in 1 month. (A ranking of "4" was defined as "Possible," i.e., <1 failure in 6 months. The observed rate in the period from October 17, 2006, through October 16, 2007, was higher than the "Possible" definition, and, therefore, fit the ranking of "Frequent."[363]) Of note, this information was known to Ethicon during the time period of FDA's review of the PROLIFT 510(k), and I found no evidence that such information was provided to FDA or that the DDSA was revisited based on the observed malfunctions in clinical practice.

For events similar to the first two described above, there is no long-term follow up information available to determine if the patients affected may have experienced prolapse recurrence or other sequelae for which the device malfunction (requiring an accommodation by the surgeon) may have been a contributing factor. The third event described above fit the "Hazard" criteria ranking of "Severe." Notably, there were multiple Issue Reports in which the surgery time was longer due to device malfunction. Accordingly, based on my synthesis and analysis of the information reviewed and discussed herein, and my knowledge, training, and experience in medical product development and adverse event reporting, a reasonably prudent medical device manufacturer would have reported these events as MDRs and proactively followed up long-term to assess whether there were any long-term consequences potentially associated with the PROLIFT malfunctions.

I also reviewed other examples where internal assessments of reported events, even if reported as MDRs, downplayed their significance, which affected the determination as to whether events were escalated for further evaluation. One example is a PROLIFT+M report of mild mesh erosion and recurrence of cystocele Stage II, reported for a clinical trial participant. The surgeon reported the event as related to the device and not related to the procedure. However, the final assessment recorded that "Based on the review of the event information, the device is not related to the event." Further, the quality and medical assessment conclusions were reviewed and no escalation was required.[364]

I reviewed a number of other Issue Reports categorized as "not reportable" that, in my professional opinion, met the criteria for submission of a MDR report. Examples are provided below:

- Medical Director received report from Doctor who reported "three patients with significant dyspareunia after the procedure. They have adequate vaginal length and depth, just very tender at the apex (post-hysterectomy patients)." In response to Ethicon's investigation, the doctor emailed the following comments: "I have had significant problems with the Prolift kit in my patients....I have 3 current patients with dyspareunia,

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[361] ETH-03533 at 560: PROLIFT Product Device Design Safety Assessment, Revision C, 2/25/2005, Appendix VI.
[362] ETH-03533 at 560: PROLIFT Product Device Design Safety Assessment, Revision C, 2/25/2005, Appendix VIII.
[363] ETH.MESH.02646594 at 598: Tracking #10100058857 – Issue Report, October 16, 2007, Alert Date.
[364] ETH.MESH.03348264-266: Issue Report Tracking #10100129770.

2 additional ones that I have taken back to the OR for excision of mesh. I have currently discontinued use of Prolift due to these concerns."[365]

The rationale for not reporting this event was "There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure. Post-operative complications can occur as a result of multiple factors, including patient characteristics, nature of treatment rendered, and various extraneous factors. There is no indication of medical or surgical intervention."[366] In fact, the last statement is false, as the doctor noted two cases that required surgery for mesh excision. Additionally, as has been previously discussed in this report, Dr. David Robinson testified that both the mesh and the surgical technique can be factors leading to erosion.[367] Further, he testified that chronic pain and dyspareunia were known complications "from the start."[368]

- Ethicon Medical Director received a complaint regarding a patient undergoing a disability evaluation after a total PROLIFT. Patient was reported to have a "constellation of symptoms including urinary incontinence, frequency, and some bowel complaints."[369]

  The case was determined to be a third party litigation. There was "no pertinent clinical information available because the reporting physician, not the operating physician placing the Prolift, is a Certified Independent Medical Examiner, who declined to provide any assistance to further our investigation."[370] Thus, the rationale for not reporting this event was as follows. "No actual device malfunction is cited. There is no evidence to suggest that the device itself caused any permanent impairment or damage to a body function or body structure. There is no indication of medical or surgical intervention. Pelvic floor with Prolift is not intended to treat or prevent urinary incontinence. Every pelvic floor repair procedure is associated with a risk of post-operative incontinence resulting from the change in the anatomical relationships of the pelvic organs and tissues. Urinary incontinece [sic], urgency and 'bowel problems' could very well be existing symptoms associated with anterior and posterior pelvic organ prolapse."[371]

  If the manufacturer becomes aware of information that reasonably suggests that its device may have caused or contributed to a serious injury, it is required to be reported to FDA. Because the contribution of the device to the events in this case could not be ruled out, and it was known from Ethicon's internal U.S. clinical study to evaluate the TVM technique that 20% of the study subjects expected urinary incontinence, it was reasonable to consider that the PROLIFT may have contributed to the reported events. And according to Dr. Robinson, "...I feel that our own data studies are the best source of AE information.[372]

[365] ETH.MESH.02646926: Tracking #10100072345 – Issue Report, April 29, 2008, Alert Date.
[366] ETH.MESH.02646926 at 928: *Id.*
[367] Dr. David Robinson deposition, 3/14/2012, 449: 20-24.
[368] Dr. David Robinson deposition, 3/13/2012, 311:2-312:12.
[369] ETH.MESH.02647100: Issue Report Tracking #10100075864, July 24, 2008, Alert Date.
[370] ETH.MESH.02647100 at 101-102: *Id.*
[371] ETH.MESH.02647100 at 103: *Id.*
[372] Dr. David Robinson deposition, 3/14/2012, 396:19-20.

The Medical Device Reporting regulations provide for just such cases. Specifically, if a manufacturer cannot submit complete information in a report, it must provide a statement explaining why this information was incomplete and the steps taken to obtain the information.[373] Of particular note, submission of a MDR does not constitute an admission that the device caused or contributed to the event(s). In fact, the manufacturer may deny that the information submitted constitutes an admission that the device caused or contributed to the reportable event(s).[374]

- Sales representative reported a surgeon seeking advice for a patient three or four months post-operative who had developed extrusion of the mesh in the urethral area. Dr. Robinson contacted the surgeon and provided the following information: the procedure was an anterior PROLIFT; patient had done well "but now has an approximately 1 cm x 1 cm exposure of mesh on the anterior wall along the previous incision line. We discussed methods of dealing with this and methods of avoidance in the future."[375]

  The Issue Report documents that "This file will remain not reportable because the sales rep has indicated that the mesh was trimmed in the Doctors Office."[376] The additional rationale provided was that this was not a reportable event, because the "event occurred post-procedure and no actual device malfunction is cited or indicated. There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure. Post-operative complications can occur as a result of multiple factors, including patient characteristics, nature of treatment rendered, and various extraneous factors."[377] Note that the latter explanation for complications is the precise rationale provided in the first example above.

  Thus, it is noteworthy that in a December 2005 email, Cary Brennan, Project Manager, Worldwide Customer Quality, following up a surgeon's report of exposure after PROLIFT with TVT, asked Dr. Robinson if he could enter his "**standard comment** about the causes of exposures with mesh" and she would put the comment in the MedWatch due that day, to which Dr. Robinson replied, "Done."[378] (Emphasis added.) Yet, for the two internal clinical studies conducted to evaluate the TVM technique, mesh exposure occurred in 10% of patients in the French study and in 14.1% of patients in the U.S. study. In Dr. Robinson's own words, "...I feel that our own data studies are the best source of AE information."[379]

Ethicon advised FDA it "reviews all complaints, including reportable adverse events on a monthly basis."[380] The meaningfulness of such a review and implementation of any appropriate corrective and preventive actions are compromised if the contribution of the device to the events is minimized or negated, as exemplified by the given examples.

[373] 21 CFR § 803.50(b)(3).
[374] 21 CFR § 803.16.
[375] ETH.MESH.02645725: Issue Report Tracking #10100024130, April 17, 2006, Alert Date.
[376] ETH.MESH.02645725 at 726: *Id.*
[377] ETH.MESH.02645725 at 728-729: *Id.*
[378] ETH.MESH.00847496-498: Email series, 28 Dec 2005, between C. Brennan, Worldwide Customer Quality, and Dr. David Robinson, Medical Director.
[379] Dr. David Robinson deposition, 3/14/2012, 396:19-20.
[380] ETH.MESH.00356982 at 985: Ethicon's K071512 S02 Submission to FDA, 9/20/07.

D. Vaginal Mesh Unmet Clinical Needs

As noted previously in this report, Ethicon held an expert meeting on meshes for pelvic floor repair on February 23, 2007.[381] The minutes of that meeting, attended by Dr. David Robinson, plus 13 others from Ethicon and seven experts, show that a "summary of unmet needs generated June 2nd 2006 was again confirmed." Among those unmet needs were the following:[382]

- No shrinkage / no long-term contraction
  Fibrosis reduction
  Severe contraction → Dyspareunia → sexual function↓
  Tension response↓
  = ↓ *Sexual pain?*
  No folding of mesh
  No rigidity
  Priority 10 (points)
- No Vaginal distortion, normal vaginal wall, maintain sexual function, normal sexual function
  Priority 8
- Elasticity simulating physiology
  Priority 5
- No chronic pain
  Priority 4
  Patient comfort
  Priority 2
  Less erosion
  Less vaginal mesh exposition
- No foreign body reaction
  Less inflammatory response
  No local inflammation
  Is there an "optimum" foreign body reaction?
  "No mesh at all is the best"(Emphasis added.)
- Low complications
  No complications
- Lack of palpable mesh in vagina

(Note that for those unmet needs listed above for which there are no priority points, that is because no priority points were shown in the Ethicon document.)

[381] ETH.MESH.02017152: Ethicon Expert Meeting: Meshes for Pelvic Floor Repair, February 23, 2007, Minutes.
[382] ETH.MESH.02017152 at 155-156: *Id.*

In my professional opinion, this is a key, significant document. It demonstrates unequivocally that Ethicon was aware that the PROLIFT mesh was fraught with all of these issues for pelvic floor repair. Yet, at the time of this meeting, the PROLIFT was on the market without 510(k) clearance, and these known unmet needs affecting patient safety were not addressed with FDA in the June 2007 510(k) (K071512) submission and subsequent 510(k) review period. Nor did dyspareunia (ranked as the highest priority of unmet needs) or pain appear in the "Adverse Reactions" listing in the Instructions for Use until October 1, 2009. Notably, the listing of "elasticity simulating physiology" as an unmet need refutes Ethicon's statement "The bi-directional elastic property allows adaptation to various stresses encountered in the body,"[383] which had been included in the Instructions for Use for multiple products for years. This document supports my previously-stated opinion that the PROLIFT was misbranded due to labeling issues. It also further supports my opinion, previously stated, that FDA would not have cleared the PROLIFT 510(k) without adequate clinical evaluation (as FDA initially requested in its August 24, 2007, letter of 510(k) deficiencies[384]), had the Agency been apprised of the adverse event issues/unmet needs listed above. Of special note is the statement documented in this list that "No mesh at all is the best."

E. PROLIFT Risk Management Report (Legacy) and Clinical Expert Report

The Risk Management Report (Legacy) (RMR) for PROLIFT summarizes the overall residual risk (ORR) associated with the PROLIFT product.[385] Based on the "Harms-Hazards Summary Table" of complaint data from January 2007 through May 2010, the Overall Residual Risk, or "Sum of Harm Frequency," was 68. This number was generated from the total of the "Estimated Frequency of Harm Rating" for each of the "Harms" listed on the Harms-Hazards Summary Table, including the following:[386]

- Unintended tissue reaction
- Blood loss
- Dermal/fascia tissue damage
- Internal organ damage
- Nerve damage/pain
- Neurological deficit
- Delayed wound healing
- Exposure – GI
- Exposure – vaginal
- Erosion – UT
- Fistula formation
- Infection
- Failure of treatment

[383] ETH.MESH.00372341 at 351: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[384] ETH.MESH.00372330 at 332: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[385] ETH.MESH.00311193 at 194: Risk Management Report (Legacy) – GYNECARE PROLIFT, Revision #1 (FM0000458, rev2).
[386] ETH.MESH.00311193 at 198: *Id.*

It is remarkable that this table of harms excludes dyspareunia and contraction, as well as urinary tract adverse events, all of which were known to Ethicon, as discussed previously in this report, and also had been reported in the two internal clinical studies conducted to evaluate the TVM technique. It is reasonable to conclude that the ORR would have exceeded 68 if these additional, known harms had been included. This is an example that shows the quality/reliability of the outcome is only as reliable as the data that are used to generate the outcome. Nevertheless, the ORR score of 68 still meant that the ORR level was High and required a risk benefit analysis. However, the "Medical Affairs Summary Statement (ORR>29)" provided the following explanation as to why the required risk benefit analysis was not done: "The Clinical Expert Report (CER_Prolift_6302010 Final.doc) prepared and signed by David Robinson, July 2, 2010, will serve to indicate Gynecare PROLIFT is a safe and effective product in lieu of a risk benefit analysis."[387] Finally, the Risk Management Report concluded that the "Overall Residual Risk is considered acceptable per the requirements defined in PR602-003."[388]

According to PR602-003, the "Company Procedure for Medical Device Risk Management Plan," [389] the Worldwide Vice President of Quality Assurance/Regulatory Affairs (WWVP QA/RA), along with the WW VP Chief Medical Officer, and WW VP R&D (or their designees, which must be at Director level or above[390]) are to approve the Risk Management Report for devices in which the ORR level is deemed "High," but for which the Benefits outweigh the Risk, as shown through an appropriate Risk Benefit Analysis.[391] For performance of the Risk Analysis, the core team is to include members with appropriate device and process knowledge from such disciplines as the following: Worldwide Quality Engineering, Medical Affairs, Product Marketing, Development Engineers, Worldwide Customer Quality, Process Engineering, Regulatory Affairs, and Clinical Affairs.[392]

The Clinical Expert Report authored by Dr. Robinson, in lieu of the risk benefit analysis, documents that the ORR indicates the need for a complete risk/benefit analysis, and a Risk/Benefit Analysis section is included in the Clinical Expert Report.[393] The Harms/Hazards Summary Table discussed above is repeated in the Clinical Expert Report,[394] along with the ORR level of "High." Dr. Robinson wrote, "As a result of this process [referring to the Risk/Benefit analysis] and a thorough review of all other pertinent information, including: a detailed clinical literature review as provided in Section C of this Report and the complaint reviews (internal and MAUDE Database) as provided in Section E, the overall residual risk associated with GYNECARE PROLIFT is considered acceptable in view of well documented benefits/patient outcomes.[395]

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[387] ETH.MESH.00311193 at 199: *Id*
[388] ETH.MESH.00311193 at 199: *Id.*
[389] ETH.MESH.00070187: Company Procedure for Medical Device Risk Management Plan, PR602-003, Revision #13.
[390] ETH.MESH.00070187 at 204: *Id.*
[391] ETH.MESH.00070187 at 192: *Id.*
[392] ETH.MESH.00070187 at 197-198: *Id.*
[393] ETH.MESH.01207154 at 174: Clinical Expert Report – Gynecare Prolift Pelvic Floor Repair System, by David Robinson, MD, FACOG, July 2, 2010.
[394] ETH.MESH.01207154 at 175: *Id.*
[395] ETH.MESH.01207154 at 176: *Id.*

Based on my knowledge, training, and professional experience in medical product development, the "thorough review" Dr. Robinson documented did not include "all other pertinent information." Specifically, it did not include a review of the MAUDE database for similar products, and, importantly, there is no reference in the Clinical Study Report to the October 2008 FDA *Public Health Notification* (PHN): "Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."[396] As discussed above regarding the RMR, a number of the adverse events known to Ethicon and also named in the FDA PHN were not included in the Risk/Benefit analysis of the Clinical Study Report, e.g., vaginal scarring, urinary problems, dyspareunia, and the requirement for additional surgical procedures due to mesh complications. Yet the Company Procedure for Medical Device Risk Management Plan instructs that the Risk Analysis is to include a review of "FDA and other databases for information concerning performance complaints for products similar in design, application or use as the device being considered."[397]

Finally, the Company Procedure for Medical Device Risk Management Plan provides options for risk reduction. Among those are the following:

- "New labeling, changes in labeling, changes in Instructions for Use (IFU), addition of warnings in labeling, and/or changes in the user training strategy.
- **Note**: Listing or inclusion within the product labeling regarding residual risk(s) should be considered when drafting the IFU (labeling) content. If residual risks are not included in the product's labeling, a rationale should be documented in the RM report."[398]

I found no evidence to indicate that Ethicon undertook any changes in labeling or user training based on the Risk/Benefit Analysis discussed in the Clinical Expert Report.

OPINION #4: Misbranding due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

The Global Harmonization Task Force (GHTF) guidance document titled, "Manufacturer's Trend Reporting of Adverse Events," instructs that "It is also important to recognize that there are circumstances when a manufacturer should take action immediately without waiting for a trend to occur. It may be based on the severity of the event, or by perceived risks associated with the adverse event(s) regardless of the number of events."[399] In contrast, Ethicon relied on an overall complaint rate determined by the total number of adverse events reported for the corresponding volume of units distributed in the reporting time period.[400] By so doing, Ethicon failed to account for underreporting of adverse events. Further, Ethicon minimized or negated the contribution of the PROLIFT device as a potential factor in a number of adverse event reports. As advised in the GHTF guidance titled, "Adverse Event Reporting Guidance for the Medical Device Manufacturer

[396] FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, Issued October 20, 2008.
[397] ETH.MESH.00070187 at 198: Company Procedure for Medical Device Risk Management Plan, PR602-003, Revision #13.
[398] ETH.MESH.00070187 at 210: *Id.*
[399] GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events, January 2003.
[400] ETH.MESH.01207154 at 171: Clinical Expert Report – Gynecare Prolift Pelvic Floor Repair System, by David Robinson, MD, FACOG, July 2, 2010.

or its Authorized Representative," "As a general principle, there should be a pre-disposition to report rather than not to report in case of doubt on the reportability of an event."[401] In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events that met the criteria for Medical Device Reporting, rendering the PROLIFT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[402] While most MedWatch reports that were submitted to FDA were submitted within the 30-day time period required by regulation, Ethicon deviated from the standard of care in a number of cases where the report was submitted to FDA well beyond the required reporting time frame. Further, no follow-up reports were identified for 88.6% of the MDR reports reviewed. In fact, the FDA notified Ethicon about its lack of follow-up with regard to the MDRs it received and Ethicon's "justification" for failing to reach a determination as to whether the complaints were related to the device. Ethicon's justification for failing to reach a determination in its reports to the FDA was that "the device was not returned for evaluation." In response, the FDA stated as follows: "We are well aware that the probability of getting back infected bloody and torn apart meshes after they are removed from the patient is minimal. For the reports of death and serious injury we need your follow up with the health care provider, accessing patient's surgery note, and follow up visits, and so on, so you can find out exactly what went wrong. Your follow up should reveal to you and to us the root cause of these reoccurring problems that have become a major concern. Is it the surgeon experience-training issue? Is it the tools with which the mesh is implanted-device issue? Is it the patient selection-labeling and warning issue?" [403] In my professional opinion, Ethicon deviated from the standard of care for a reasonably prudent medical device manufacturer by taking a passive rather than a pro-active approach to follow-up of MDR reports.

Importantly, in my professional opinion, Ethicon failed to interpret the adverse event data for the PROLIFT in the context of the seriousness of the disability resulting from certain of the injuries and the requirement for additional surgical intervention. As discussed in this report, of the 968 MDR reports retrieved and reviewed based on the independent search described, 68.2% (660) reported the need for follow-up surgery as a result of the reported events. Based on the totality of the information available to Ethicon, as discussed in this report, it is my professional opinion that the conclusion reached in the PROLIFT Risk Management Report[404] that the PROLIFT is a safe and effective product, based on the July 2010 Clinical Expert Report, in lieu of a risk benefit analysis, was faulty. Dr. Robinson's conclusion in the Clinical Expert Report that the "overall residual risk associated with GYNECARE PROLIFT is considered acceptable in view of well documented benefits/patient outcomes" [405] is inconsistent with the overall assessment of risk/benefit in the medical literature in my professional opinion; significantly, it is also inconsistent with FDA's review of the applicable literature as discussed in the 2011 FDA *Safety Communication*. Specifically, while most published studies agree that the use of mesh increases the cure rate based on objective criteria, that has not been comprehensively correlated with patient-

[401] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative, June 29, 1999.
[402] FDCA § 502(t).
[403] ETH.MESH.00079755 at 756: May 8, 2008, Ethicon Letter to Nasrin Mirsaidi, FDA, CDRH Medical Device Reporting, RE: Response to request for information, March 21 and 24, 2008.
[404] ETH.MESH.00311193 at 199: Risk Management Report (Legacy) – GYNECARE PROLIFT, Revision #1 (FM0000458, rev2).
[405] ETH.MESH.01207154 at 176: Clinical Expert Report – Gynecare Prolift Pelvic Floor Repair System, by David Robinson, MD, FACOG, July 2, 2010.

reported quality of life outcomes. When these have been reported, there is little difference between surgical procedures using mesh and those without mesh, and the use of mesh is associated with additional complications, particularly mesh erosion.

Furthermore, most published reports of clinical trials have only included a short-term follow-up. Thus, Dr. Robinson's "Literature Review Conclusion Statement," provided following, in the Clinical Expert Report is inconsistent with the lack of long-term safety and efficacy studies in the literature: "The above data [referring to his literature review], taken together with any available pre-clinical data, are sufficient to demonstrate compliance with the essential requirements covering safety and performance of GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems under normal conditions of use. **No additional clinical data is required**."[406] (Emphasis added.) Moreover, this statement is contradicted by FDA's later issuance of orders mandating postmarket surveillance studies.

In my professional opinion, based on the information known or knowable to Ethicon, a reasonably prudent medical device manufacturer would have undertaken pro-actively the appropriate, controlled clinical studies to identify the patient population, if any, for which the potential risks were justified by the potential benefit in anatomic outcome, using the PROLIFT. Additionally, reasonably prudent efforts to manage risk would have included labeling changes, specifically, to add Warnings and Precaution to the Instructions for Use, including the following:

- Warning that patients may require additional surgical procedure(s) to repair mesh erosion, which may be debilitating;
- Warning that complications have been shown to be higher with mesh placement compared to traditional non-mesh repair;
- Precaution that while transvaginal repair with mesh may provide anatomic benefit compared to traditional, non-mesh POP repair, this may not result in better symptomatic results.

Because Ethicon judged the risk acceptable, no such actions were taken to manage the risks. In my professional opinion, Ethicon continued to market a product that was misbranded due to labeling issues, in particular, as a result of inadequate directions for use and inadequate warnings, and because the device was dangerous to health when used in the manner suggested in the labeling.[407]

IX. SUMMATION OF OPINIONS: STANDARD OF CARE AND DEVIATIONS

OPINION #1: Ethicon Marketed a Misbranded and Adulterated PROLIFT Device

The FDCA requires that a medical device be 510(k)-cleared[408] or approved[409] by FDA prior to introduction of the device into interstate commerce, except when a change made to an existing 510(k)-cleared device does not pose the potential to significantly affect the safety or

[406] ETH.MESH.01207154 at 170: *Id.*
[407] FDCA § 502(f)(1) and (2) (21 USC § 352).
[408] FDCA §§ 510(k), 513(i).
[409] FDCA § 515

effectiveness of the device or the intended use of the device.[410] In my professional opinion, Ethicon marketed a misbranded and adulterated PROLIFT device from the time of its product launch in early 2005 until 510(k) clearance was obtained.[411] Even thereafter, Ethicon continued to disseminate false and misleading information in the form of its IFUs, Patient Brochures and other marketing information with regards to the safety and effectiveness of the PROLIFT System.

OPINION #2: Ethicon Reported False and Misleading Information to FDA

During the review of the PROLIFT 510(k) (K071512/01), Ethicon failed to disclose to FDA known safety issues with the PROLIFT, as discussed above. Not only did Ethicon not disclose safety issues but Ethicon also reported to FDA that the PROLIFT did not introduce any new issues of safety or effectiveness as compared to the GYNEMESH predicate and "that surgeons can use the device without problems."[412] In my professional opinion, Ethicon submitted false and misleading information to FDA, in violation of the standard of care required of a medical device manufacturer.

OPINION #3: PROLIFT Misbranded - Failure to Warn and False or Misleading Labeling

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. For this reason, a device manufacturer must implement label changes in a timely manner as soon as possible after notice of any issues that may impact the safety or effectiveness of the device.[413] While labeling for prescription devices is premised on the concept that prescription devices are not safe for use except under the supervision of a licensed practitioner and, accordingly, are exempt from the "adequate directions for use" requirements applicable to OTC devices,[414] prescription device labeling nevertheless is required to contain information adequate for a licensed practitioner to use the device safely and effectively for its intended use.[415] Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[416]

In my professional opinion, based on my review of the PROLIFT labeling history and the IFU and patient labeling information discussed in this report, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of multiple labeling issues. Section 502 of the FDCA contains provisions on misbranding and the labeling issues that cause a product to be misbranded.

[410] 21 CFR § 807.81(a)(3).
[411] ETH.MESH.00748451: Substantial Equvalence Letter for Prolift and Prolift+M Total, Anterior, and Posterior Pelvic Floor Repair Systems, May 15, 2008.
[412] ETH.MESH.00372341 at 347: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.
[413] Bryan Lisa deposition, 12/19/11, 293:12-294:18.
[414] 21 CFR § 801.109
[415] 21 CFR § 801.109(c).
[416] 21 CFR § 801.109(d).

OPINION #4: Misbranding due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

The Global Harmonization Task Force (GHTF) guidance document titled, "Manufacturer's Trend Reporting of Adverse Events," instructs that "It is also important to recognize that there are circumstances when a manufacturer should take action immediately without waiting for a trend to occur. It may be based on the severity of the event, or by perceived risks associated with the adverse event(s) regardless of the number of events." [417] In contrast, Ethicon relied on an overall complaint rate determined by the total number of adverse events reported for the corresponding volume of units distributed in the reporting time period.[418] By so doing, Ethicon failed to account for underreporting of adverse events. Further, Ethicon minimized or negated the contribution of the PROLIFT device as a potential factor in a number of adverse event reports. In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events that met the criteria for Medical Device Reporting, rendering the PROLIFT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[419] In my professional opinion, Ethicon deviated from the standard of care for a reasonably prudent medical device manufacturer by taking a passive rather than a pro-active approach to follow-up of MDR reports.

Importantly, in my professional opinion, Ethicon failed to interpret the adverse event data for the PROLIFT in the context of the seriousness of the disability resulting from certain of the injuries and the requirement for additional surgical intervention. Further, based on the information known or knowable to Ethicon, a reasonably prudent medical device manufacturer would have undertaken pro-actively the appropriate, controlled clinical studies to identify the patient population, if any, for which the potential risks were justified by the potential benefit in anatomic outcome, using the PROLIFT. Additionally, reasonably prudent efforts to manage risk would have included labeling changes, specifically, to add Warnings and Precaution to the Instructions for Use, including the following:

- Warning that patients may require additional surgical procedure(s) to repair mesh erosion, which may be debilitating;
- Warning that complications have been shown to be higher with mesh placement compared to traditional non-mesh repair;
- Precaution that while transvaginal repair with mesh may provide anatomic benefit compared to traditional, non-mesh POP repair, this may not result in better symptomatic results.

Because Ethicon judged the risk acceptable, no such actions were taken to manage the risks. In my professional opinion, Ethicon continued to market a product that was misbranded due to labeling issues, in particular, as a result of inadequate directions for use and inadequate warnings, and because the device was dangerous to health when used in the manner suggested in the labeling.[420]

[417] GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events, January 2003.
[418] ETH.MESH.01207154 at 171: Clinical Expert Report – Gynecare Prolift Pelvic Floor Repair System, by David Robinson, MD, FACOG, July 2, 2010.
[419] FDCA § 502(t).
[420] FDCA § 502(f).

X. CONCLUSIONS

Based on my professional experience, knowledge, and training, and my review and evaluation of the information identified and discussed in this report, including the materials and scientific/medical literature specified in Appendices B. through E., it is my professional opinion, to a reasonable degree of scientific and professional probability, that Ethicon violated those duties required of a reasonably prudent medical device manufacturer. As discussed in this Report, Ethicon released to physicians PROLIFT devices that were both adulterated and misbranded until May 15, 2008, due to failure to have 510(k) clearance. Ethicon withheld known adverse event information and known problems with physician training on the PROLIFT transvaginal mesh technique from the FDA during 510(k) review, such that it is my professional opinion that FDA would not have cleared the PROLIFT System without appropriate clinical evaluation had the Agency been apprised of these issues. Based on the safety issues that have been observed with the device through clinical experience, the likelihood of clearance, if appropriate clinical studies had been done, is questionable. At a minimum, expanded safety information, including warnings and potential consequences of use, would have been required for product labeling.

The devices were misbranded due to multiple labeling issues, including false and misleading information, inadequate directions for use, inadequate warnings, and because the devices were dangerous to health when used in the manner suggested in the labeling. The devices were misbranded due to a failure to reveal material facts as to the consequences that might result from use of the device. Finally, the PROLIFT devices were misbranded because of Ethicon's failure to submit MDR reports for a number of adverse events that qualified for reporting under Section 519 of the FDCA. While Ethicon reviewed the scientific and medical literature and FDA's MAUDE database for the PROLIFT, the company failed to respond to the signals about which it became aware, not only from these sources but also from other information directly reported to Ethicon (e.g., by its consultants and in clinical study reports) and available on FDA's MAUDE database for similar products of other manufacturers.

As a consequence of these multiple failures, Ethicon marketed a product that violated safety and ethical standards. Both the physicians using the PROLIFT System and the patients in whom these devices were used lacked the necessary information to make an informed decision about the risks versus the benefit of using this device instead of an alternative method of treatment. Accordingly, the standard of care for the protection of the rights, safety, and welfare of patients was violated, thus disrupting the regulatory process and the protections that exist specifically to safeguard the public health.

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Peggy Pence, PhD, RAC, FRAPS

July 17, 2014
Date